# Single Technology Appraisal

# Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Servier:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Bowel Cancer UK

4. **External Assessment Report** prepared by Aberdeen HTA Group
   a. External Assessment Report
   b. Addendum

5. **External Assessment Report – factual accuracy check**
   a. EAG report – factual accuracy check
   b. Addendum – factual accuracy check

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

## Document B

## Company evidence submission

**December, 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| [ID6298]_Lonsurf_bev_mCRC_DocB_ [redacted] | 1.0 | Yes | December 2023 |



# Contents





# Tables and figures





# Abbreviations

| Abbreviation | Description |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 3L | Third-line |
| 5-FU | Fluorouracil |
| AE | Adverse events |
| AFT | Acceleration failure time |
| AIC | Akaike information criteria |
| ASCO | American Society of Clinical Oncology |
| BIC | Bayesian information criteria |
| BID | Twice daily |
| BNF | British National Formulary |
| BRAF | V-raf murine sarcoma viral oncogene homolog B1 |
| BSA | Body surface area |
| BSC | Best supportive care |
| CAPOX | Capecitabine, oxaliplatin |
| CEAC | Cost-effectiveness acceptability curve |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | Confidence interval |
| CIMP | CpG island methylator phenotype |
| CIN | Chromosomal instability |
| CR | Complete response |
| CRC | Colorectal cancer |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | Disease control rate |
| DMMR | DNA mismatch repair |
| DOR | Duration of response |
| DSU | Decision Support Unit |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EMBASE | Excerpta Medica database |
| eMIT | Electronic market information tool |
| EORTC QLQ-C30 | European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire |
| EQ-5D-5L | EuroQol-5 Dimension-5 levels |
| ESCAT | Scale for Clinical Actionability of Molecular Targets |
| ESMO | European Society Medical Oncology |

| Abbreviation | Description |
|---|---|
| FAS | Full analysis set |
| FDG-PET | Fluorodeoxyglucose-positron emission tomography |
| FOLFIRI | 5-FU, leucovorin, and irinotecan |
| FOLFOX | 5-FU, leucovorin, and oxaliplatin |
| FOLFOXIRI | 5-FU, leucovorin, oxaliplatin, and irinotecan |
| FTD/TPI | Trifluridine-tipiracil |
| GHS | Global health status; |
| HER2 | Human epidermal growth factor receptor 2 |
| HNPCC | Hereditary nonpolyposis colorectal cancer |
| HR | Hazard ratio |
| HRQoL | Health-Related Quality of Life |
| IA | Investigator-assessed |
| ICER | Incremental cost-effectiveness ratio |
| IMP | Investigational medicinal product |
| INMB | Incremental net-monetary benefit |
| IRC | Independent review committee |
| ITT | Intention to treat |
| IV | Intravenous; |
| KM | Kaplan-Meier |
| KRAS | Kirsten Rat Sarcoma proto-oncogene GTPase |
| LCHP | Log cumulative hazard plots |
| LYG | Life years gained |
| mAB | Monoclonal antibody |
| MCBS | Magnitude of Clinical Benefit Scale |
| mCRC | Metastatic colorectal cancer |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MRI | Magnetic resonance imaging |
| MSI | Microsatellite instability |
| NCC | National Cost Collection |
| NHB | Net-health benefit |
| NMA | Network meta-analysis |
| NRAS | Neuroblastoma rat sarcoma viral oncogene homolog |
| ONS | Office of National Statistics |
| ORR | Objective response rate |
| OS | Overall survival |
| OWSA | One-way sensitivity analysis |
| PartSA | Partitioned survival analysis |
| PAS | Patient access scheme |
| PD | Progressive disease |
| PFS | Progression-Free survival |
| PH | Proportion hazards |

| Abbreviation | Description |
|---|---|
| PICOS | population, interventions, comparators, outcomes, and study design |
| PO | Oral |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PR | Partial response |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| PSM | Parametric survival models |
| PSS | Personal Social Services |
| PSSRU | Personal Social Services Research Unit |
| QALY | Quality-adjusted life years |
| QoL | Quality of life |
| QQ | Quantile-quantile |
| RAS | Rat sarcoma virus |
| RCT | Randomised Controlled trial |
| RDI | Relative dose intensity |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | Serious adverse events |
| SD | Standard deviation |
| SS | Safety set |
| SLR | Systematic literature review |
| SmPC | Summary product characteristics |
| TA | Technology appraisal |
| TEAE | Treatment-related emergent adverse events |
| ToT | Time on treatment |
| TP53 | Tumour protein p53 |
| TSD | Technical Support Document |
| TTD | Time to treatment discontinuation |
| TWiST | Prior to disease progression without adverse events |
| USG | Ultrasonography |
| VEGF | Vascular endothelial growth factor |
| WT | Wild-type |
| WTP | Willingness-to-pay |

## B.1 Decision problem, description of the technology and clinical care pathway

### *B.1.1 Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| Population | Adults with metastatic colorectal cancer after 2 systemic treatments | Adults with metastatic colorectal cancer after 2 systemic treatments | |
| Intervention | Trifluridine–tipiracil with bevacizumab | Trifluridine–tipiracil with bevacizumab | |
| Comparator(s) | • Single-agent irinotecan (after FOLFOX)<br>• FOLFIRI (after either FOLFOX or CAPOX)<br>• FOLFOX (after either FOLFIRI or CAPOX)<br>• Raltitrexed (if 5-FU/FA are not suitable)<br>• Trifluridine–tipiracil monotherapy • Regorafenib<br>• Nivolumab with ipilimumab (where high microsatellite instability or mismatch repair deficiency is present)<br>• Encorafenib with cetuximab (if BRAF V600E mutation-positive metastatic colorectal cancer)<br>• Best supportive care | Servier considers the following comparators to be appropriate:<br>• Trifluridine–tipiracil monotherapy<br>• Regorafenib<br>• Best Supportive care | Servier do not consider all comparators listed in the scope to be appropriate.<br>• Single-agent irinotecan (after FOLFOX)<br>• Raltitrexed (if 5-FU/FA are not suitable)<br>In technology appraisal TA914[1] with pembrolizumab, the company stated that irinotecan and raltitrexed were excluded based on clinical feedback that they are rarely used in practice unless other treatments are contraindicated. The clinical expert and Cancer Drugs Fund lead both confirmed that irinotecan and raltitrexed monotherapy are rarely used in clinical practice.<br>• FOLFIRI (after either FOLFOX or CAPOX)<br>• FOLFOX (after either FOLFIRI or CAPOX) |

| | | | |
|---|---|---|---|
| | | | These are second line settings so should not be used as a comparator to Trifluridine/tipiracil + bevacizumab as the SmPC states for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have received two prior anti-cancer treatment regimens. Both the inclusion criteria of SUNLIGHT[2] and the SPC (mentions; including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.<br>• Nivolumab with ipilimumab (where high microsatellite instability or mismatch repair deficiency is present)<br>Technology appraisal TA914[1] with pembrolizumab states 4-8% of patients with colorectal cancer have MSI-H tumours. CHECKMATE 142[1] publication, references "patients with DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) mCRC to ≈4% to 5% of patients." However, only around 35 people per year are expected to have nivolumab with ipilimumab for colorectal cancer with high MSI or MMR deficiency. This number is small because pembrolizumab is already available as a first-line therapy and people can only have a |



| | | | |
|---|---|---|---|
| | | | checkpoint inhibitor at one point in the treatment pathway.<br>An advisory board carried out by Servier Laboratories in July 2023[3] and clinical insight meetings[4], it was found that clinicians would use nivolumab with ipilimumab in the second line setting prior to the use of Trifluridine-tipiracil + bevacizumab, and therefore earlier in the treatment pathway.<br>This regimen is used if genetic testing indicates high microsatellite instability or mismatch repair deficiency. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens.<br>• Encorafenib with cetuximab<br>An advisory board carried out by Servier Laboratories in July 2023[1] and clinical insight meetings[4] found that clinicians would use encorafenib with cetuximab in the second line setting prior to the use of trifluridine-tipiracil + bevacizumab, and therefore earlier in the treatment pathway. |

| | | | |
|---|---|---|---|
| | | | This regimen is used if genetic testing indicates BRAF V600E mutation-positive. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens. |
| Outcomes | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life | |
| Subgroups to be considered | If the evidence allows the following subgroups will be considered. These include:<br>• People without prior bevacizumab | People without prior bevacizumab | |

**Key:** 5-FU, fluorouracil; CAPOX, capecitabine, oxaliplatin; dMMR, DNA mismatch repair deficient; EMA, European Medicines Agency; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX; fluorouracil, leucovorin, and oxaliplatin; mCRC: metastatic colorectal cancer; MMR, mismatch repair; MSI-H, microsatellite instability-high; SmPC, summary of product characteristics



## *B.1.2 Description of the technology being evaluated*

A description of trifluridine-tipiracil with bevacizumab is presented in Table 2. The current summary of product characteristics (SmPC) is provided in Appendix C.

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Trifluridine-tipiracil (Lonsurf) with bevacizumab (Avastin) |
| **Mechanism of action** | Trifluridine-tipiracil has a unique mechanism of action compared with other fluorinated antimetabolites, which accounts for its activity against tumours that are resistant to 5-FU and similar drugs.<br>Trifluridine is a thymidine-based nucleoside analogue, analogue that is incorporated into the DNA of tumour cells and inhibits tumour growth.<br>Tipiracil hydrochloride is a thymidine phosphorylase inhibitor lows the breakdown of trifluridine to prolong its action.<br>Bevacizumab is the first anti-angiogenic therapy that binds to all circulating VEGF-A isoforms. It prevents the interaction of VEGF-A with VEGFR, inhibiting the activation of VEGF signalling pathways that promote neovascularization |
| **Marketing authorisation/CE mark status** | Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anti-cancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.[5] |
| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have received two prior anti-cancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.[5] |
| **Method of administration and dosage** | Lonsurf is an oral tablet supplied in two dosage strengths:<br>• 15 mg/6.14 mg film-coated tablet (15 mg trifluridine/6.14 mg tipiracil)<br>• 20 mg/8.19 mg film-coated tablet (20 mg trifluridine/8.19 mg tipiracil)<br>Lonsurf is available in aluminium blister packs of 20, 40, or 60 film-coated tablets |

| | |
|---|---|
| | *When Lonsurf is used in combination with bevacizumab for the treatment of CRC, the recommended dose of Lonsurf is 35 mg/m$^2$/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle for as long as benefit is observed or until unacceptable toxicity occurs.<br>Bevacizumab is administered by intravenous infusion and supplied in two compositions (Each ml of concentrate contains 25 mg of bevacizumab):<br>• Each 4 ml vial contains 100 mg of bevacizumab<br>• Each 16 ml vial contains 400 mg of bevacizumab<br>*When bevacizumab is used in combination with Lonsurf for the treatment of CRC, the recommended dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks |
| **Additional tests or investigations** | None |
| **List price and average cost of a course of treatment** | Trifluridine-Tipiracil:<br>Lonsurf Film-Coated Tabs 15/6.14 mg (60 tabs)=£1500<br>Lonsurf Film-Coated Tabs 15/6.14 mg (20 tabs)=£500<br>Lonsurf Film-Coated Tabs 20/8.19 mg (60 tabs)=£2000<br>Lonsurf Film-Coated Tabs 20/8.19 mg (20 tabs)=£666.67<br>Bevacizumab Cost per 14 days £852.95 BNF (vegzelma)<br>Average cost per course of treatment £3692.40 |
| **Patient access scheme (PAS) if applicable** | PAS simple discount already in place for trifluridine-tipiracil applies. Company is unsure of the cost of bevacizumab treatment under a PAS |

**Key**: BNF: British National Formulary; CRC; colorectal cancer; EGFR; estimated glomerular filtration rate; mg; milligram; PAS: patient access scheme; VEGF, vascular endothelial growth factor

## *B.1.3 B1.3 Health condition and position of the technology in the treatment pathway*

The survival rates for CRC are significantly lower for patients diagnosed at Stage IV compared with earlier stages of disease with 1-year survival rates of approximately 44%. In addition, 5-year survival rates for patients with metastases are 10% in the UK. Survival outcomes in the ≥ 3L setting are particularly poor, ranging between 6–12 months.

Although curative surgery is preferred, most patients with mCRC have incurable, unresectable disease. Therefore, treatment goals in unresectable mCRC focus on delaying tumour progression, relieving tumour-related symptoms, optimising survival, maintaining quality-of-life (QoL) , and minimising chemotherapy-related toxicity.

The proposed place in therapy of trifluridine-tipiracil plus bevacizumab is alongside trifluridine-tipiracil monotherapy and regorafenib, where trifluridine-tipiracil in combination with bevacizumab has been awarded a score MCBS 4, higher than any of the other treatments available at 3rd line in the most recent update to the ESMO guidelines.

Patients now have an opportunity to benefit from a combination treatment that is highly effective (an additional 3.3 months compared to trifluridine-tipiracil monotherapy) with a favourable safety profile and a positive QoL impact. In addition to the compelling clinical case, the confidential discount on trifluridine-tipiracil (that was increased further in 2022, prior to its reimbursement in gastric cancer), ensures it is value for money for the NHS.

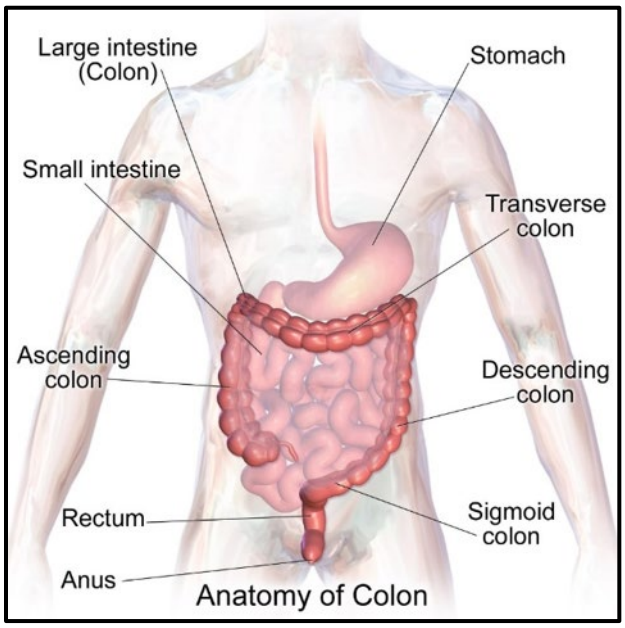
The unmet need is significant and the case Is strong for a quick decision-making process to approve this combination and bring about a step change to the care pathway for metastatic CRC patients in order to add those valuable extra months to life.

### B.1.3.1 Disease overview

Colorectal cancer (CRC) involves the large intestine and the rectum, the lowest part of the digestive system (Figure 1).[6] Colon cancer accounts for 72% of CRCs and rectal cancer for 28% of CRCs[7], although these tumours are generally considered as a single tumour entity rather than separate cancer types.[8] 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 cecum, ascending colon, and transverse colon.[9]

**Figure 1: Diagram of the colon and rectum**

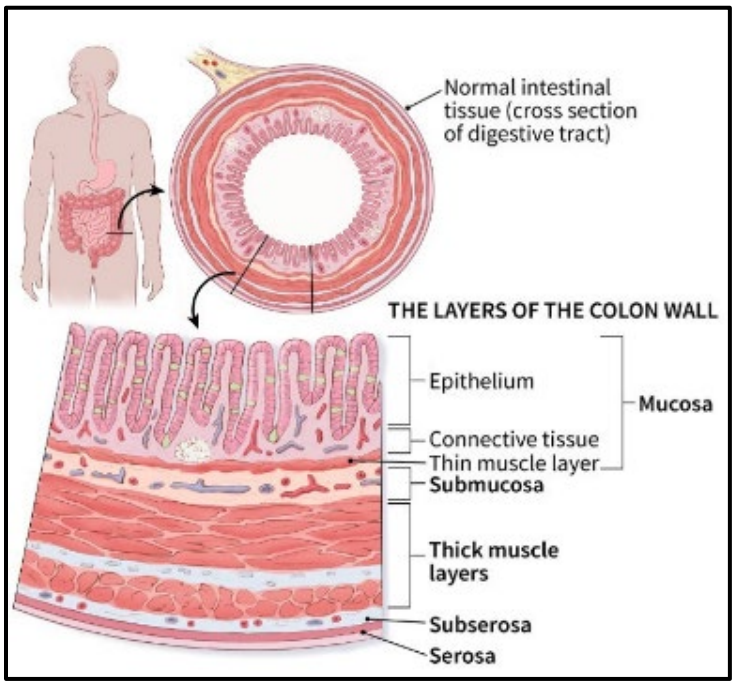



**Source**: (Blausen.com 2014)[10]

The majority of CRCs typically begin as a benign polyp in the colon or rectum wall that gradually transform into a malignant cancer over 10-15 years.[6,8] Colorectal polyps are very common, with polyps found in around 50% of individuals over the age of 50 years. However, not all polyps develop into cancer.[11]

Most CRC are adenocarcinomas.[12] Once a CRC has formed, it can gradually invade the different layers of the wall of the colon or rectum over time. CRC typically starts in the innermost layer, or the mucosa, and progresses outward through some or all of the other layers (Figure 2). The CRC can also spread to nearby blood vessels or lymph nodes, and then onwards to other lymph nodes or to distant parts of the body. The stage (extent of spread) of CRC depends on how deeply the tumour grows into the wall and if the cancer has spread outside the colon or rectum. The earliest stage CRCs are classed as Stage 0, and then range from Stage I-IV, where Stage IV refers to metastatic CRC (mCRC) that has spread to other organs and tissues beyond the colon or rectum.[13]

**Figure 2: The layers of the colon wall**

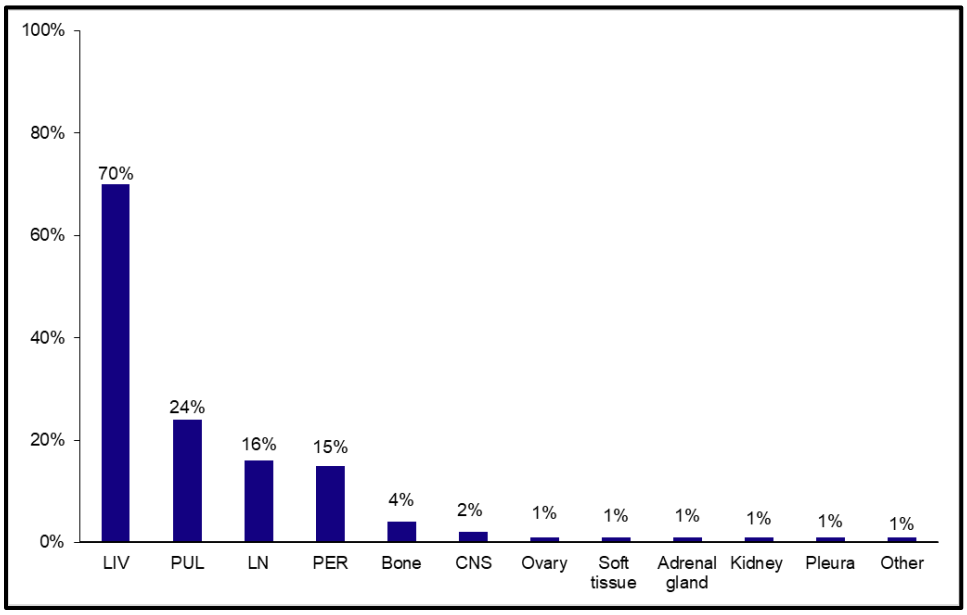



**Source**: (American Cancer Society 2020)[13]

The most common location for metastases associated with CRC are the liver, lung, and peritoneum (Figure 3).[14,15] Metastatic sites such as bone, spleen, brain, and distant lymph nodes have also been described.[16,17] The anatomical location and histological subtype of the CRC affect the pattern of metastases:

- Metastases in the thorax, nervous system, and bone are more frequently associated with rectal cancer [14]
- Metastases in the peritoneum are more frequently associated with colon cancer[14]
- Metastases in the liver and lung are more often associated with left-sided colon cancer[18]

**Figure 3: Involved anatomical sites in patients with first presentation of mCRC (Germany, 2007-2014, n=385)**




**Source:** Adapted from (Holch 2017)[15]

**Notes**: The study was a retrospective cohort study involving 385 patients in a university in Germany between 2007 and 2014

**Key**: CNS: central nervous system; LIV: liver; LN: distant lymph nodes; mCRC: metastatic colorectal cancer; PER: peritoneum; PUL: pulmonary (lungs)

CRC is a heterogenous disease, with the clinical and molecular characteristics of each tumour determining the prognostic outcome and response to treatment[19]. Genomic instability is an important feature underlying CRC, where the progressive accumulation of genetic and epigenetic alterations over time drives the transformation of normal colonic epithelium to benign adenomas, which then progresses to invasive and metastatic malignant adenocarcinomas.[20]

There are three different genomic pathways that lead to CRC[21]:

- **Chromosomal instability (CIN)**–- The CIN pathway is considered to be the classical pathway, representing up to 80%-85% of all CRC cases.[22] CIN tumours are recognised by the accumulation of mutations in specific oncogenes, including Kirsten Rat Sarcoma proto-oncogene GTPase (*KRAS*) and v-raf murine sarcoma

viral oncogene homolog B1 (*BRAF*), as well as in tumour suppressor genes such as adenomatous polyposis (*APC)* and tumour protein p53 (*TP53*).[20]

- **Microsatellite instability (MSI)** – MSI occurs in 15%-20% of sporadic CRC and in >95% of hereditary nonpolyposis CRC (HNPCC), also known as Lynch syndrome, an inherited form of CRC.[20] CRC tumours are classified based on the number of microsatellites exhibiting instability. Tumours are classified as MSI high (MSI-H) when ≥30% of the markers exhibit instability. CRC with <30% markers exhibiting instability are defined as MSI low (MSI-L), and tumours with no apparent instability are microsatellite stable (MSS).[20,21]

- **CpG island methylator phenotype (CIMP)** – CIMP accounts for approximately 15% of sporadic cases and are almost exclusively associated with MSI CRC tumours. CIMP provides the epigenetic instability necessary for sporadic cancers to methylate the promoter regions, therefore, inactivating the expression of key tumour suppressor genes like mutL homolog 1 (*MLH1).* There is a strong association between CIMP-positive cancers and *BRAF* mutation.[20]

#### *B.1.3.1.1 Risk factors*

Most CRCs are sporadic (70%), with a minority of genetic mutations leading to CRC being inherited (5%) or familial (25%).[23] The biggest risk factor for CRC is increasing age, with lifestyle factors playing an important role (Table 3).[24]

**Table 3: Risk factors associated with CRC**

| Risk Factors | Explanation |
|---|---|
| ***Patient characteristics*** | |
| Age | Increasing age is the biggest risk factor for CRC. The risk of developing CRC drastically increases past 50 years of age and about 90% of new CRC cases occur in people over the age of 50 years |
| Gender | Men have a 30% higher risk of developing CRC than females. Women are more prone to right-sided colon cancer which is often diagnosed at a more advanced stage |
| Race | Non-Hispanic Black individuals have the highest incidence rate of CRC of all racial groups: approximately 50% higher than in Asians and about 20% higher than in non-Hispanic Whites |

| Risk Factors | Explanation |
|---|---|
| Socioeconomic Factors | It has been shown that people with low socioeconomic status generally have a higher risk of developing CRC. This may be explained by limited access to healthcare services and treatment resources, and unhealthy dietary habits, sedentary lifestyle, and smoking in the low socioeconomic status population |
| ***Family History*** | |
| Familial | CRC may occur in more than one member of the same family but not be hereditary. Multiple family members on one side of the same family may be diagnosed with CRC, and in familial CRC, the cancer usually occurs later in life and does not follow the same patterns that are seen in hereditary CRC. Familial CRC is not caused by a change in one gene, but results from multiple different influences impacting the same family |
| Inherited | Inherited CRC is defined as a genetic mutation that is present from birth, passed from a mother or a father to a child. There is usually a pattern of CRC on one side of the family. It is estimated that 2%-8% of CRC arise as a result of inherited syndromes. The two most common hereditary syndromes that predispose for CRC are HNPCC (also known as Lynch syndrome) and FAP |
| ***Medical History*** | |
| IBD | Ranked as the third-highest risk condition for developing CRC after HNPCC and FAP. Chronic inflammation promotes tumour growth and progression, therefore individuals with IBD have about a 2 to 6 times greater risk of developing CRC. The risk of CRC increases with the duration of IBD and the anatomic extent and severity of the disease |
| Colon Polyps | Histologically classified into two main categories: non-neoplastic and neoplastic (adenomatous). The adenomatous polyps have the potential to become malignant and it is estimated that about 95% of CRC is developed in adenomatous polyps. The risk of malignancy increases with the polyp size, degree of dysplasia and the age of the patient |
| Diabetes Mellitus | Individuals with type 2 diabetes have 2 to 3 times greater risk of developing CRC |
| ***Lifestyle*** | |
| Diet – Red and Processed Meat | Red meat and processed meat are classed as probably carcinogenic to humans. It is estimated that the risk of CRC increases by about 17% for every 100 grams of red meat and approximately 18% for every 50 grams of processed meat eaten daily |
| Diet – Fibre, Fruit, and Vegetables | A diet low in fibre, fruit and vegetables is associated with increased risk of CRC. It is estimated that high consumption of dietary fibre could reduce the risk of CRC by up to 50% |
| Diet – Calcium, Vitamin D, and Dairy Products | The high consumption of dairy products (in particular milk) has been suggested as having a protective effect against CRC. This is largely attributed to calcium. Calcium was found to inhibit proliferation and to induce apoptosis of tumour cells. Additionally, the other milk component, vitamin D, has been suggested to play a beneficial role against CRC |

| Risk Factors | Explanation |
|---|---|
| Obesity | Overweight/obese men and women have about 50% and 20% greater risk of developing CRC. It is estimated that an overall CRC risk increases by 3% for every 5 kg of weight gained |
| Physical Inactivity | It is estimated that physically inactive people have up to 50% higher risk of developing CRC |
| Smoking | People who smoke cigarettes have a 2 to 3-fold increase of developing CRC and the risk increases with dose and duration of exposure. Additionally, it is considered that smoking makes up 12% of CRC deaths |
| Alcohol Consumption | It is estimated that the alcohol consumption of two to three drinks daily increases the risk of CRC by about 20% and drinking more than three alcoholic drinks increases the risk by about 40% |
| ***Other*** | |
| Gut Microbiota | According to recent research that explored the microbiome in CRC individuals, alternation in the composition and functionality of the normal gut microbiota may lead to initiation, promotion, and progression of CRC |

**Source**: (Sawicki 2021)[24]

**Key**: CRC: colorectal cancer; FAP: familial adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer; IBD: inflammatory bowel disease

#### *B.1.3.1.2 Burden to patients, carers, and society*

CRC has a significant negative impact on many aspects of a patient's QoL. CRC negatively affects social functioning, including work and productive life, relationship with friends and family, and other social activities and interests[25]. The stage and site of CRC at diagnosis influences patient QoL, since these factors determine both the symptoms experienced (which differ according to tumour site and presence of metastases) as well as the treatments used and duration of therapy (with associated adverse events [AE])[26].

Patients diagnosed with mCRC have a short life expectancy and often spend half of their remaining life with disability[26]. A study estimated that 35.3% of patients with mCRC worked full or part-time compared to 45.2% of patients who were no longer able to work due to illness. Symptoms such as fatigue, drowsiness, memory problems, and neuropathy were all associated with patients stopping work[27].

Family caregivers of patients with CRC often face a range of stressors, including occupational and financial strain, family role changes, disrupted household routines, and their own mental and physical health problems[28]. At advanced stages of CRC, the burden becomes even greater. The disease may be especially distressing for caregivers as they cope with the patient's high physical

symptom burden and uncertain or poor prognosis. Awareness of the inevitability of disease progression and death may contribute to caregivers' depressive and anxiety symptoms. One US study conducted individual, semi-structured qualitative interviews with 23 patients with advanced CRC and 23 primary family caregivers.[28] The results identified four key challenges affecting caregivers: (1) emotionally processing the initial diagnosis or reoccurrence, (2) managing practical and emotional aspects of patient care, (3) facing an uncertain future, and (4) encountering symptom-related suffering.[28]

#### *B.1.3.1.3 Epidemiology*

CRC is the fourth most common cancer in the UK; there were 34,825 new cases in England in 2017, which accounted for 11% of all new cancer cases. The current incidence of CRC in England is 77 incidence cases per 100,000 [29]

Around 4 in 10 (43%) new cases of colorectal cancer in the UK were in people aged over 75 years, but it can affect young people too.[30]

Stage IV metastatic CRC (mCRC) is an advanced form of CRC that has metastasized beyond the large intestine and nearby lymph nodes, typically spreading first to the liver.[30] Patients with Stage IV mCRC have a poor prognosis, with 1-year survival rates of approximately 44%, and 5-year survival rates of less than 10%.[30] Survival outcomes in the ≥ 3L setting are particularly poor, ranging between 6–12 months.[31]

#### *B.1.3.1.4 Prognosis*

The site of the primary tumour influences prognosis.[14] Left-sided mCRC has a better response to current available systemic therapies than right-sided mCRC.[32] The observed differences in treatment response may be attributed to the distinct tumour biology of right and left-sided tumours[32]:

- 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 MSI-H and a higher tumour mutational burden, 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.[32]

Prognosis is also strongly related to the stage of the disease at diagnosis and the number and location of distant metastases.[14] Metastasis is the leading cause of cancer-related mortality in CRC, and most patients that have mCRC have incurable disease.[33] For patients diagnosed with mCRC, 56% die within a year compared with only 2% of patients diagnosed with Stage I CRC (UK data, collected 2013-2017).[30] Five-year net survival for CRC shows a much larger difference in survival between Stage I and Stage IV: in males, 5-year net survival declines from 91% at Stage I to 10% at Stage IV and in females 5-year net survival declines from 93% at Stage I to 10% at Stage IV (UK data, collected 2013-2017).[30]

#### *B.1.3.1.5 Diagnosis of CRC*

CRC can be discovered at any stage, from asymptomatic cancer identified by screening through to presentation as a surgical emergency[34]:

- The first opportunity to diagnose CRC is through routine screening.
- Currently, the most common route to diagnosis is through a primary care visit with non-urgent symptoms.
- CRC may also be diagnosed during a medical emergency. Approximatively 25% of cases present in this way, typically due to bowel obstruction or perforation. While the majority of patients with bowel obstruction have had symptoms for a very short period of time, a subset of them have had persistent symptoms prior to the emergency presentation.

The simplest method of CRC recognition is via rectum examination, where 70% of rectal cancers and 30% of CRCs are recognised.[35] The most frequent and efficient method of CRC diagnosis is through endoscopy, which includes sigmoidoscopy and colonoscopy[36]. These procedures allow the healthcare professional to localise the tumour and take part of the large intestine for histological examination. Imaging tests including roentgenographic examination of the thorax, endorectal ultrasonography (USG), abdominal USG, computed tomography (CT), and nuclear magnetic resonance imaging (MRI) are also valuable diagnostic tools.[35]

Physical examination, blood counts, and renal and liver function tests are used to determine if the CRC has progressed to metastatic disease.[37] Clinical or biochemical suspicion of mCRC is then confirmed by radiological imaging, usually a CT, MRI, or ultrasound scan. Additionally, a fluorodeoxyglucose-positron emission tomography (FDG-PET) can be an effective tool in determining the malignant characteristics of the tumoral lesions, especially when combined with a CT scan. This technique is particularly useful in determining the extent of the metastatic disease.

The assessment of tumour histology, including both the primary location and any metastases, is necessary before initiating a systemic therapy.[38] Testing for mismatch repair (MMR)/MSI status and *KRAS*, *NRAS* exon 2, 3, and 4, and *BRAF* mutation is recommended in all patients with mCRC at the time of metastatic diagnosis, which can be conducted on either the primary tumour or any metastatic site. *RAS* mutations are negative predictive factors for the use of anti-EGFR monoclonal antibodies, and therefore *RAS* testing is mandatory before this treatment is initiated. *BRAF* mutation status should be assessed simultaneously with *RAS* for prognostic assessment, although is not mandatory. dMMR/MSI testing is also recommended (but not mandatory) for its predictive value in determining the use of immune checkpoint inhibitors.[38]

#### *B.1.3.1.6 Unmet need in the treatment of mCRC*

The 5-year survival rates for CRC are significantly lower for patients diagnosed at Stage IV compared with earlier stages of disease.[30] 5-year survival rates for patients with metastases are 10% in the UK.[30]

Although curative surgery is preferred, most patients with mCRC have incurable, unresectable disease.

The treatment of mCRC can entail a range of approaches, including surgery, radiotherapy, systemic therapy, and supportive care[38]:

- Surgical intervention is preferred if it is considered that the mCRC is potentially resectable leaving no tumour at the margin, with the curative goal of both removing primary tumour and any metastases.

- However, most patients with mCRC have disease that is not initially suitable for potentially curative resection. For these patients it is crucial to identify unresectable disease that could potentially become operable after a significant response to systemic therapy. The primary objective of treatment in this case is to transform the initially unresectable cancer into a resectable and potentially curable one.

- Most patients with mCRC present with unresectable disease that cannot be converted to resectable disease through systemic treatment. For these patients, the objective of treatment is to control disease progression and prolong life, while maintaining QoL.

Therefore, treatment goals in unresectable mCRC focus on delaying tumour progression, relieving tumour-related symptoms, optimising survival, maintaining QoL, and minimising chemotherapy-related toxicity.

The treatment of unresectable mCRC should be tailored to each patient's specific needs and should plan to improve tumour-related symptoms, delay progression, and prolong

survival in metastatic disease not amenable to definitive surgical treatment or local treatments along with maintaining QoL and minimising chemotherapy-related toxicity.[38]

### B.1.3.2 Clinical pathway of care

#### *B.1.3.2.1 First-line treatment*

First-line (1L) treatment for patients with mCRC typically involves a doublet chemotherapy in combination with a targeted biologic agent.

*Doublet or triplet chemotherapy*

In the 1L treatment setting, the doublet chemotherapy typically contains a fluoropyrimidine backbone with irinotecan or oxaliplatin, such as:

- Fluorouracil (5-FU), leucovorin, and oxaliplatin [FOLFOX] or
- 5-FU, leucovorin, and irinotecan [FOLFIRI]

In selected fit patients without significant comorbidities the cytotoxic triplet of 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) may be used. Due to the more severe side-effects associated with triplet chemotherapy, this regimen should not be used in patients >75 years of age, patients with performance status (PS) ≥2, or in patients with significant comorbidities.[38]

The oral fluoropyrimidine capecitabine can be used as an alternative to IV 5-FU/leucovorin (both alone and in combination with oxaliplatin [CAPOX]). Since capecitabine is an oral prodrug it provides an effective and convenient treatment option for patients with mCRC, which may improve adherence to treatment and overall QoL.

*Targeted biologic therapy*

Several targeted agents have demonstrated improved outcomes when combined with chemotherapy The biologic used in the combination varies based upon the mutation profile and location of the tumour[38]:

- For patients with left-sided mCRC RAS WT disease, the preferred 1L treatment is a cytotoxic doublet in combination with an anti-EGFR antibody (cetuximab or panitumumab). Cetuximab and panitumumab are less effective in the presence of RAS mutations, which can lead to resistance to treatment. Therefore, it is crucial to determine the RAS-mutational status of a patient before initiating treatment to avoid unnecessary treatment and potential adverse effects in these patients.

- For patients with mCRC and right-sided RAS WT disease or a tumour harbouring RAS-mutation, the preferred 1L treatment is a cytotoxic doublet plus bevacizumab.

- In patients with mCRC and dMMR/MSI-H tumours, pembrolizumab in has demonstrated benefit and is recommended as standard of care.

- In frail or elderly patients, unable to tolerate chemotherapy, whose tumours are left-sided and RAS WT, anti-EGFR antibody can also be administered as monotherapy.

#### *B.1.3.2.2 Second-line treatment*

The choice of second-line (2L) therapy for mCRC is influenced by the treatments administered in 1L:

- FOLFIRI or FOLFOX are the typical chemotherapy backbone options for 2L treatment, depending on the 1L systemic therapy received (for example, patients receiving FOLFOX in 1L could receive FOLFIRI in 2L, while patients receiving FOLFIRI in 1L could receive FOLFOX or CAPOX in 2L). The addition of bevacizumab for bevacizumab-naïve patients or ‘beyond-progression’ (where a patient's cancer continues to grow or spread despite receiving bevacizumab as part of their treatment), has demonstrated benefit compared with chemotherapy alone although the National Institute for health and Care Excellence (NICE) guidance states bevacizumab in combination with oxaliplatin and either

fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.[39]

- In *RAS* WT mCRC tumours that have not received any prior anti-EGFR therapy, cetuximab or panitumumab can both be considered in 2L therapy in combination with FOLFIRI.[40]

- In dMMR/MSI-H tumours progressing after 1L chemotherapy, NICE approved the use of ipilimumab plus nivolumab.[41]

2L treatment is common in mCRC, with more than 60% of patients from 1L receiving a 2L regimen.[42]

#### *B.1.3.2.3 Third-line treatment*

Figure 4 summarises the treatment algorithm recommended by ESMO.

Trifluridine-tipiracil plus bevacizumab is recommended in all patients, irrespective of *KRAS* or *BRAF* mutation [I, A; ESMO-MCBS v1.1 score: 4].[38,43]

Trifluridine-tipiracil is recommended in all patients, irrespective of *KRAS* or *BRAF* mutation [I, A; ESMO-MCBS v1.1 score: 3].[38] In TA405, NICE approved the use in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-epidermal growth factor receptor (EGFR) agents, or when these therapies are not suitable.[44]

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 rechallenging of treatments.[37] However, clinical insights given to the company are that rechallenge should not be seen as an additional line of treatment. For example, one clinician reported that trifluridine-tipiracil monotherapy or regorafenib would be the

only comparators. Any other chemotherapy would be re-treatment and not a new therapy and if they progress on the treatment previously, would not then give again until 5th/6th line.[4]

Regorafenib is also recommended in the ESMO guidelines [I, A, ESMO-MCBS v1.1 score: 1].[38] NICE have recommended regorafenib as an option for metastatic colorectal cancer in adults who have had previous treatment (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) or when these treatments are unsuitable.[45] When choosing between these two agents, ESMO guidelines recommend that the patient's characteristics and comorbidities should be considered, as well as the different toxicity profiles of the different agents.

In addition, best supportive care (BSC) could also be considered according to clinical insights given to the company although this is not included in ESMO guidelines. However, clinicians stated this would be more for those patients who were PS 2+.[4]

Encorafenib with cetuximab is mentioned in the ESMO guidelines for those with BRAF V600E mutation. An advisory board carried out by Servier Laboratories in July 2023[1] and clinical insight meetings[4] found that clinicians would use encorafenib with cetuximab in the second line setting prior to the use of trifluridine-tipiracil + bevacizumab, and therefore earlier in the treatment pathway. This regimen is used if genetic testing indicates the patient's disease is BRAF V600E mutation-positive. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens.

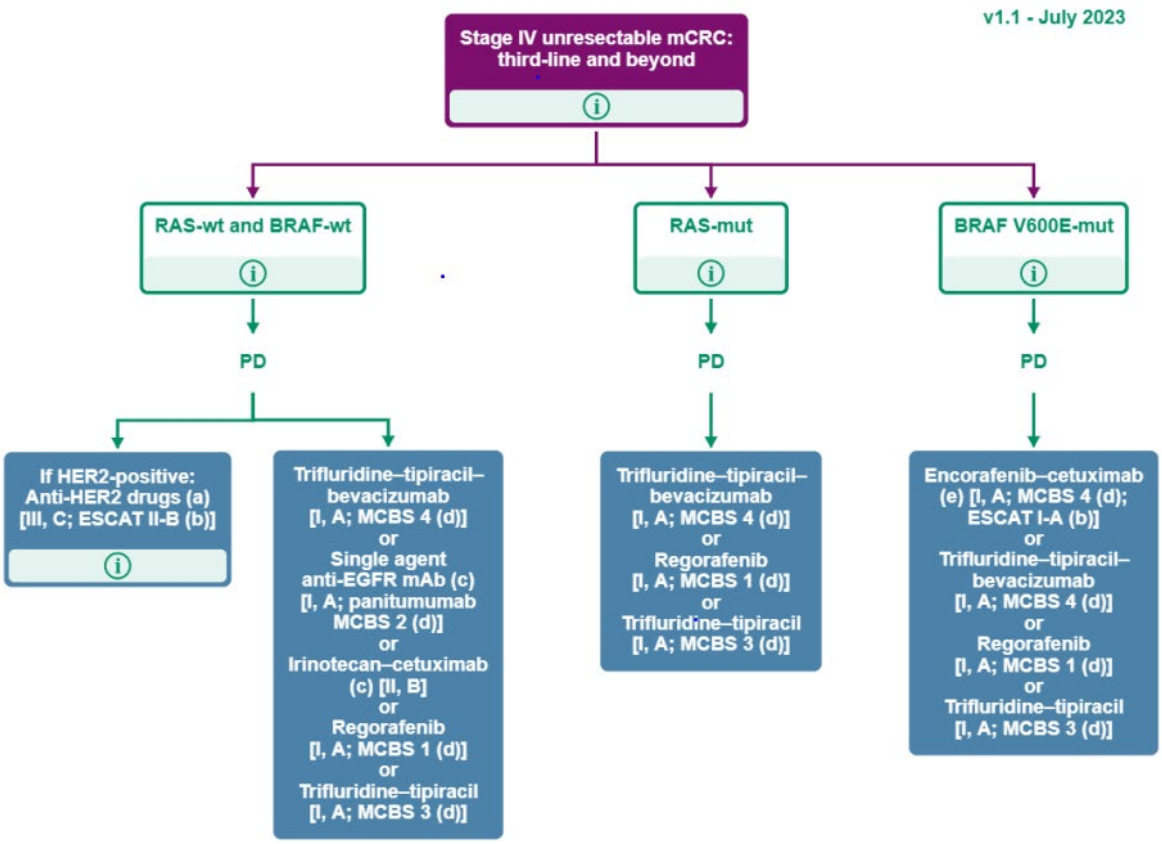
The NICE scope also mentions nivolumab with ipilimumab (where dMMR/MSI-H is present). Technology appraisal TA914[1] with pembrolizumab states 4-8% of patients with colorectal cancer have MSI-H tumours. The CheckMate 142[1] publication, references patients with dMMR/MSI-H) mCRC to ≈4% to 5% of patients

However, only ~35 people per year are expected to have nivolumab with ipilimumab for colorectal cancer with high MSI or MMR deficiency. This number is small because pembrolizumab is already available as a first-line therapy and people can only have a checkpoint inhibitor at one point in the treatment pathway. Findings from an advisory board carried out by Servier Laboratories in July 2023[3] and clinical insight meetings[4], found that clinicians would use nivolumab with ipilimumab in the second line setting prior to the use of trifluridine-tipiracil plus bevacizumab, and therefore earlier in the treatment pathway. This regimen is used if genetic testing indicates MMR/MSI-H. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil plus bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens.

**Figure 4: ESMO treatment algorithm: management of stage IV unresectable mCRC in 3L and beyond[38]**




**Source**: (Cervantes 2023)[38,43]

**Key**: 3L: third-line; anti-EGFR mAb: anti-epidermal growth factor receptor monoclonal antibody; BRAF V600E: V600E mutation in the BRAF gene; ESCAT: Scale for Clinical Actionability of Molecular Targets; ESMO: European Society for Medical Oncology; HER2: human epidermal growth factor receptor 2; MCBS: Magnitude of Clinical Benefit Scale; mCRC: metastatic colorectal cancer; PD: progressive disease; RAS: Rat sarcoma virus; WT: wild type

Figure 5 illustrates the treatment pathway for mCRC in England, based on guidance issued by NICE across all technology appraisals. In the NHS in England, treatment decisions for mCRC are based on genetic testing (biomarker driven) and treatment in later lines is informed by prior therapy. First and second-line treatment of mCRC is dominated by chemotherapy combination regimens, which are typically FOLFOX or CAPOX, and less commonly FOLFOXIRI (oxaliplatin, leucovorin, 5-FU, and irinotecan) which accounts for only 10% of all front-line treatments for mCRC). For patients with

specific mutations, clinicians have the additional choice of including immunotherapies in the first-line and second-line setting (Figure 5).

**Figure 5: UK mCRC schematic treatment management**

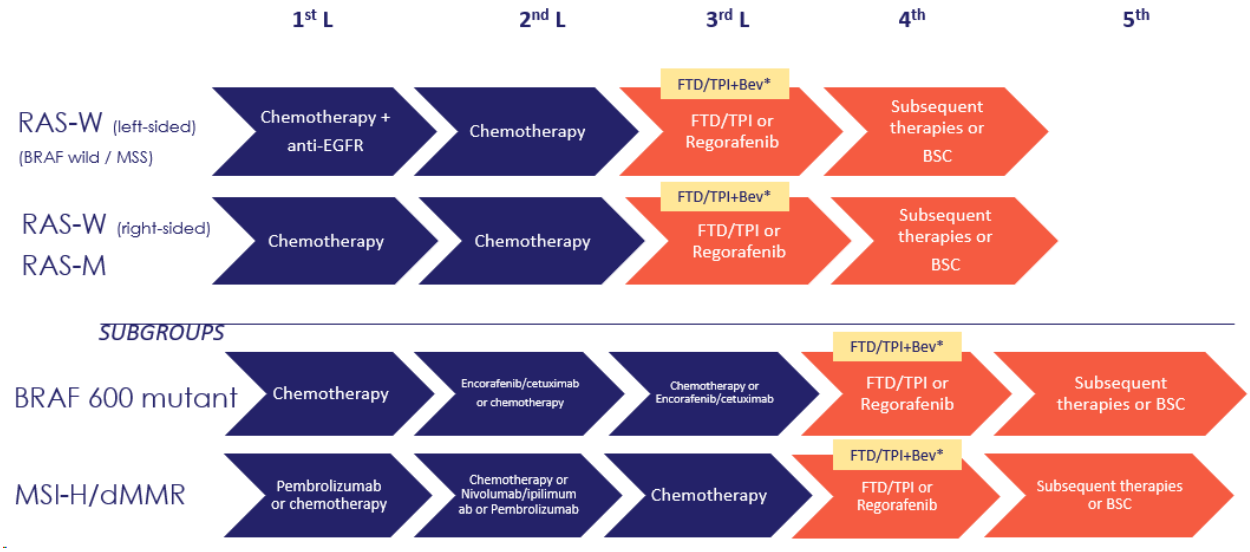



Figure adapted from NICE guidance and feedback of mCRC Therapy Area Experts.[3,4]
Chemotherapy can be FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5-FU, oxaliplatin/ irinotecan).
**Key:** BSC, Best Supportive Care; FTD/TPI+Bev, trifluridine/tipiracil + bevacizumab

Following guidance to the company by clinicians, the line of treatment of where trifluridine-tipiracil plus bevacizumab fits in is complex. The clinicians advise that the position should be more adapted to an option for mCRC in adults who have had previous treatment (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy) or when these treatments are unsuitable, which aligns with trifluridine-tipiracil monotherapy[44] and regorafenib guidance[45], rather than line of treatment.[4]

### *B.1.4 Equality considerations*

None

## B.2 Clinical effectiveness

The SUNLIGHT trial was an open-label, multinational, randomised, controlled two-arm Phase 3 trial that investigated the efficacy and safety of trifluridine-tipiracil + bevacizumab vs. trifluridine-tipiracil 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, and provides the relevant efficacy and safety data in this population.

The median OS was 10.8 months (95% CI: 9.36, 11.83) for the trifluridine-tipiracil plus bevacizumab arm versus 7.5 months (95% CI: 6.34, 8.57) for the trifluridine-tipiracil monotherapy group. The improvement in median OS with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy resulted in a hazard ratio (HR) of 0.61 (95% CI: 0.49, 0.77; p<0.001) , corresponding to 39% relative reduction in the relative risk of death.

Trifluridine-tipiracil plus bevacizumab also resulted in a clinically and statistically significant improvement in progression-free survival (PFS) compared to trifluridine-tipiracil 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. Trifluridine-tipiracil plus bevacizumab resulted in an increase of 3.2 months median PFS, a greater than two-fold increase versus trifluridine-tipiracil monotherapy (5.6 months [95% CI: 4.5, 5.9] vs. 2.4 months).

Cancer-related QLQ-C30 and general EQ-5D-5L were collected in the SUNLIGHT trial and indicated that health-related quality of life (HRQoL) was maintained for the two patient groups from baseline to Cycle 6. No clinically relevant changes in mean scores were observed in any of the sub-domains. Therefore, patients treated with both trifluridine-tipiracil plus bevacizumab and with trifluridine-tipiracil monotherapy did not show increased symptom burden over time.

Overall, there were no new safety signals or unexpected toxicities with the trifluridine-tipiracil plus bevacizumab combination. Trifluridine-tipiracil plus bevacizumab has demonstrated a manageable safety profile, consistent with the individual safety profiles of each product.

A network meta-analysis was carried out to compare with the additional comparators of regorafenib and BSC. This analysis indicates that trifluridine-tipiracil plus bevacizumab has statistical superiority over placebo/BSC, trifluridine-tipiracil, and regorafenib for both OS and PFS.

### *B.2.1 Identification and selection of relevant studies*

The systematic literature review (SLR) was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and NICE guidance for systematic reviews.[13,14] Study eligibility criteria were defined in terms of the population, interventions, comparators, outcomes, and study design (PICOS) structure outlined Table 4. The target population was patients undergoing third-line treatment for metastatic CRC, 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.

**Table 4: Clinical effectiveness SLR inclusion/exclusion criteria**

| Criteria | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Population | Adult (18+ years) patients with metastatic CRC<br>Unresectable adenocarcinoma of the colon or rectum<br>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:<br>Early-stage CRC<br>Received fewer than two prior chemotherapy regimens (i.e., first- or second-line)<br>ECOG performance status scores of 2 or higher |
| Interventions | Any of the following treatments delivered alone or in combination with each other:<br>Aflibercept<br>Best supportive care<br>Bevacizumab<br>Capecitabine<br>Cetuximab<br>Encorafenib<br>Fluorouracil<br>Fruquintinib<br>Irinotecan<br>Oxaliplatin<br>Panitumumab<br>Ramucirumab<br>Regorafenib<br>FTD/TPI (TAS-102, LONSURF) | Surgical intervention without systemic treatment<br>Radiation without chemotherapy |
| Comparators | Placebo | -- |

| Criteria | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| | Any intervention listed above<br>Investigator's choice of therapy if options are among the interventions listed above | |
| Outcomes | Efficacy outcomes:<br>Overall survival<br>Progression-free survival<br>Time to progression<br>Duration of response<br>Objective response rate<br>Time to deterioration in ECOG performance status ≥2<br><br>Safety outcomes:<br>Drug-related adverse events (AEs)<br>Grade 3-5 AEs (all, drug-related)<br>Serious AEs<br>Discontinuation due to AEs<br>Death due to AEs | -- |
| Study design | Randomised controlled trials<br>Non-randomised trials<br>Single-arm trials | Observational studies<br>Animal or *in vitro* studies<br>Case series/case reports<br>Editorials, commentaries, letters, reviews |
| Language | English | -- |
| Time | 2010 – present | -- |

**Key:** AEs, adverse events; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; FTD/TPI, trifluridine-tipiracil

### B.2.1.1 Study identification

#### *B.2.1.1.1 Database searches*

Relevant trials were identified by searching the following databases through the Ovid platform on February 10, 2023: Excerpta Medica database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Cochrane Central Register of Controlled Trials (CENTRAL). Publications were identified by the search strategies presented in Appendix D, 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 randomised controlled trials (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 metastatic CRC 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 hand-searching conference websites or published proceedings:
- American Society of Clinical Oncology (ASCO) Annual Meeting (2021-2022)
- ASCO Gastrointestinal Cancers Symposium (2021-2022)
- European Society for Medical Oncology (ESMO) Congress (2021-2022)
- ESMO World Congress on Gastrointestinal Cancer (2021-2022)
- Clinical trial registries. The US 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.

#### B.2.1.2Study 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.

#### B.2.1.3Data 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-randomised 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, performance status (e.g., Eastern Cooperative Oncology Group [ECOG]), primary tumour location and sidedness, histological subtype, number of metastatic sites, prior treatment for advanced or metastatic disease, and biomarker status (i.e., KRAS/neuroblastoma rat sarcoma viral oncogene homolog (NRAS) mutation, BRAF mutation, dMMR/ 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% confidence interval [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)); overall response rate (ORR), disease control rate (DCR), and numbers of patients with complete response, partial response, stable disease, or progressive disease; and time to deterioration in ECOG performance status ≥2.

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

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

#### B.2.1.4Study quality assessment

Risk of bias in included RCTs was assessed by two independent reviewers using the Cochrane Risk of Bias tool, version 2,[18] which assesses risk of bias in five domains (bias arising from the randomisation 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 signalling questions to an overall judgement). Quality assessment of non-randomised 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.

#### B.2.1.5Results

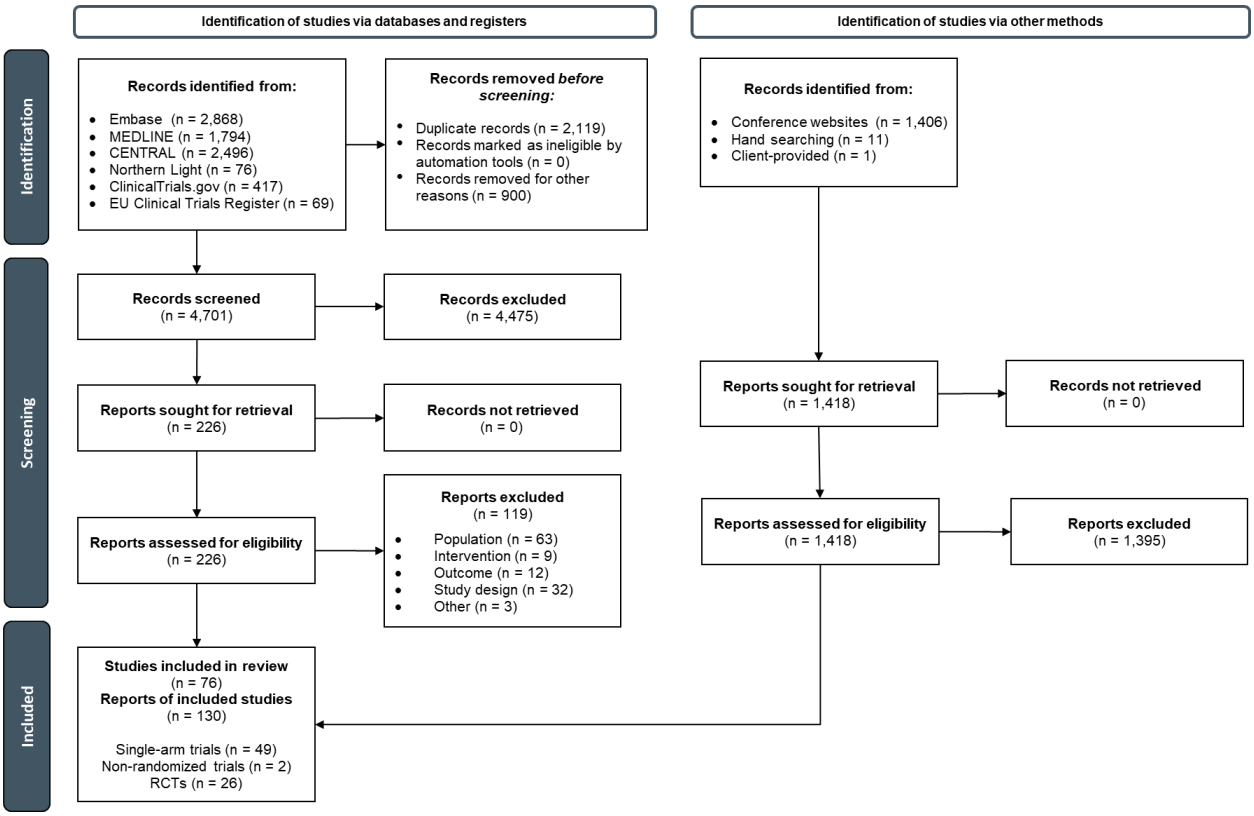
##### *B.2.1.5.1 Study selection*

Searches of Embase, MEDLINE, CENTRAL, Northern Light, and clinical trial registries identified a total of 7,720 records (Figure 6). After the removal of duplicate records and

irrelevant publication types, 4,701 titles/abstracts were screened, resulting in the identification of 226 reports for full-text review. Of these, 119 reports were excluded (Appendix D). After adding 23 reports obtained from searching conference websites, hand-searching, a total of 130 reports describing 76 unique studies were included in the SLR (Appendix D). Of these 76 studies, 26 were RCTs, two were non-randomised trials, and 49 were single-arm trials.

**Figure 6: Study selection flow diagram**




## Randomised controlled trials

### Trial characteristics

Twenty-six RCTs were identified with at least one treatment arm of interest (i.e., meeting the intervention criteria in Table 1). Thirteen trials were phase II, 12 were phase III, and one was phase II/III (Appendix D). One trial was quadruple-blind, two were triple-blind, seven were double-blind, and 16 were open-label. All trials were multicentre.

Twelve of the trials were multinational, two were conducted across the Asia continent, and the others were conducted within a single country (United States, n = 4 trials; Italy, n = 2 trials; Japan, n = 2 trials; China, n = 2 trials; United Kingdom, n = 1 trial; and Denmark, n = 1 trial).

All RCTs enrolled adult patients with locally advanced, metastatic/stage IV, or unresectable CRC (Appendix D). Nineteen trials restricted enrolment to patients with an ECOG performance status (or equivalent) of 0 or 1, and seven trials allowed the enrolment of patients with a performance status of 2. Trials varied in their enrolment criteria concerning both the number of prior lines of therapy and the treatment regimens previously received for advanced/metastatic disease.

Treatment characteristics

The 26 RCTs evaluated a total of 28 different active treatment regimens (Appendix D). The most common of which were FTD/TPI (n = 6 trials), cetuximab (n = 5 trials), cetuximab + irinotecan (n = 5 trials), panitumumab (n = 3 trials), regorafenib (n = 3 trials), fruquintinib (n = 2 trials), and FTD/TPI + bevacizumab (n = 2 trials)

Patient characteristics

Across RCTs, median patient age ranged from 49.5 to 68 years (Appendix D). Six trials enrolled predominately (~80% or more) White patients, three trials enrolled exclusively (100%) Asian patients, and the remaining trials enrolled patients with a more balanced distribution across race/ethnicity categories or did not report patient race/ethnicity. Most trials only enrolled patients with an ECOG performance status of 0 or 1, whereas seven trials enrolled some patients (between 2% and 23.5%) with a performance status of 2.

There was variation among RCTs in the numbers of prior lines of therapy that patients received for advanced/metastatic disease. Although all trials enrolled at least some patients who received two prior lines of therapy (i.e., meeting the population criteria in Table 1), some trials also enrolled patients with fewer or more than two prior lines of therapy (Appendix D). There was also variation among trials in the treatment regimens

previously received by patients (reported in Appendix D). For instance, in 17 trials, all or nearly all patients received prior oxaliplatin, irinotecan, and fluoropyrimidine; in five trials, all or nearly all patients received prior bevacizumab; in 11 trials, no patients received prior anti-epidermal growth factor receptor therapy (e.g., cetuximab, panitumumab); and in four trials, no patients received prior regorafenib.

Additional patient characteristics are provided in Appendix D, including primary tumour location (i.e., colon vs. rectum), tumour sidedness (i.e., left vs. right), number of metastatic sites, and biomarker status (i.e., dMMR/MSI-H, NRAS/KRAS mutation, BRAF mutation, and HER2 amplification).

Reported outcomes

Efficacy outcomes are reported in Appendix D. Across RCTs, median OS ranged from 4.6 months (cetuximab + BSC) to 24.7 months (cetuximab + irinotecan) (n = 23 trials), and OS rates ranged from 33% (cetuximab + BSC) to 71% (encorafenib + cetuximab + binimetinib) at 6 months (n = 4 trials) and 16% (cetuximab + BSC) to 77.2% (cetuximab + irinotecan + placebo) at 12 months (n = 5 trials) . Median PFS ranged from <1 month (placebo + BSC) to 11.3 months (cetuximab + irinotecan □ FOLFOX-4) (n = 24 trials) (Appendix D, Table D10). ORR ranged from 0% (multiple treatments) to 50% (cetuximab + irinotecan FOLFOX-4) (n = 23 trials), DCR ranged from 7% (regorafenib) to 81% (FTD/TPI + panitumumab) (n = 15 trials), and median DOR ranged from 0 months (placebo) to 18.4 months (panitumumab + BSC) (n = 8 trials) . Only one trial (SUNLIGHT) reported time to deterioration in ECOG performance status ≥2.

Therapeutic outcomes

Across the RCTs identified in the SLR, median time on treatment ranged from 5.7 weeks (placebo) to 23 weeks (cetuximab + irinotecan + placebo) (n = 13 trials) . Seven trials reported the types of subsequent therapies received and/or the proportion of patients who went on to receive subsequent therapy. No trials reported time to initiation of subsequent therapy. Outcomes are reported in Appendix D

Safety outcomes

Across RCTs, the proportion of patients who experienced any AE, grade ≥3 AEs, or SAEs ranged from 51.9% (placebo) to 100% (multiple treatments) (n = 13 trials), 10.4% (placebo) to 80.8% (cetuximab + irinotecan + vemurafenib) (n = 14 trials), and 5.8% (placebo) to 49.6% (dalotuzumab (weekly) + cetuximab + irinotecan) (n = 14 trials), respectively (Appendix D). The proportion of patients who experienced any treatment-related AE, grade ≥3 treatment-related AEs, or treatment-related SAEs ranged from 15% for placebo to 100% for cetuximab (n = 8 trials), 7.3% (multiple treatments) to 93.6% (fruquintinib + BSC) (n = 8 trials), and 1.5% (placebo) to 26% (atezolizumab + cobimetinib) (n = 6 trials), respectively. The proportions of patients who discontinued treatment or died due to AEs ranged from 0% (cetuximab + irinotecan) to 24.4% (dalotuzumab [twice weekly] + cetuximab + irinotecan) (n = 14 trials) and 0% (atezolizumab) to 16% (dalotuzumab [twice weekly] + cetuximab + irinotecan) (n = 12 trials), respectively (Appendix D).

Risk of bias

Thirteen trials had a low risk of bias, and 12 trials had some concerns of bias mostly related to the randomisation process. One trial had a high (i.e., uncertain) risk of bias due to its results being reported only in conference abstract format, which provided little methodological detail.

**Non-randomised and single-arm trials**

Of the 76 included trials, two were non-randomised trials and 49 were single-arm trials. Trial characteristics, efficacy and safety outcomes, and results of quality assessment for these trials are provided in Appendix D.

### *B.2.2 List of relevant clinical effectiveness evidence*

The relevant clinical effectiveness data for trifluridine-tipiracil plus bevacizumab comes from the phase 3 SUNLIGHT study NCT04737187.

## *B.2.3 Summary of methodology of the relevant clinical effectiveness evidence*

### B.2.3.1 Study design

The SUNLIGHT trial was an open-label, multinational, randomised, controlled two-arm Phase 3 trial that investigated the efficacy and safety of trifluridine-tipiracil plus bevacizumab versus trifluridine-tipiracil 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.[46] 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).

Patients were randomly assigned 1:1 to receive either trifluridine-tipiracil plus bevacizumab or trifluridine-tipiracil monotherapy, given as 28-day treatment cycles. During the study, administration of further anti-cancer therapy, treatment discontinuation, or treatment switching between the two study arms could have occurred.

The end of study was planned 19 months after the first investigational medicinal product (IMP) intake of the last patient randomised and defined as the date of the last follow-up of the last patient or the date of the last contact attempt if the last patient was declared lost to follow-up.

#### *B.2.3.1.1 Inclusion/exclusion criteria*

The key inclusion and exclusion criteria for SUNLIGHT are presented in Table 5.

**Table 5: Key inclusion and exclusion criteria in the SUNLIGHT trial**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| ✓ Age ≥18 years<br>✓ Histologically confirmed unresectable mCRC<br>✓ Prior treatment with ≤2 chemotherapy regimens for mCRC† and disease | × Prior treatment with >2 chemotherapy regimens for mCRC, or with Lonsurf<br>× Unresolved grade ≥3 non-haematologic toxicity related to previous chemotherapy regimen |

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| progression or intolerance to the last regimen<br>✓ 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<br>✓ Known *RAS*-mutation status<br>✓ Ability to swallow oral tablets<br>✓ Estimated life expectancy ≥12 weeks<br>✓ ECOG performance status ≤1<br>✓ Adequate bone marrow, renal, hepatic and coagulation function‡<br>✓ If applicable, negative pregnancy test and agreement to use highly effective contraception§ | (excluding alopecia and skin pigmentation)<br>× CNS metastases that are unstable or require increasing doses of steroids for control<br>× Major surgery within 4 weeks before randomisation<br>× Gastrointestinal disease that could potentially interfere with study drug absorption<br>× Severe or uncontrolled active acute or chronic infection<br>× Evidence of infection with HIV, hepatitis B virus or hepatitis C virus<br>× Uncontrolled diabetes mellitus, hypertension, or cardiac arrhythmia<br>× Active (or history of) interstitial lung disease or pulmonary hypertension<br>× Major adverse cardiovascular event within six months before randomisation, severe/unstable angina, or NYHA class III or IV heart failure<br>× Malignant disease other than mCRC<br>× Systemic immunosuppressive therapy, except steroids given prophylactically or at chronic low dosage (≤20 mg/day prednisone equivalent)<br>× Radiotherapy within four weeks before randomisation, except for palliation<br>× Serious nonhealing wound, ulcer or bone fracture<br>× Deep vein thrombosis event within four weeks before randomisation<br>× Known clinically relevant coagulopathy, bleeding diathesis or bleeding event within four weeks before randomisation |

**Source**: (Tabernero 2021)[47]

**Notes**: †Including adjuvant/neoadjuvant chemotherapy if cancer recurred either during treatment or within 6 months of its completion. ‡Absolute neutrophil count ≥1.5 × 109/l; haemoglobin 9 g/dl; platelet count ≥100 × 109/l; creatinine clearance ≥50 ml/min; total serum bilirubin 1.5 × ULN; alanine and aspartate



aminotransferase levels ≤2.5 × ULN (≤5 × ULN in patients with liver metastases). §Contraception criterion applies to women of childbearing potential and men with partners of childbearing potential

**Key**: ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; mCRC, metastatic colorectal cancer; NYHA, New York Heart Association; ULN, upper limit of normal

### B.2.3.2Primary and secondary endpoints

The primary endpoint for the SUNLIGHT trial was OS (Prager 2023b). Secondary endpoints included PFS, ORR, and DCR, safety and tolerability, and the impact on QoL of trifluridine-tipiracil plus bevacizumab compared to trifluridine-tipiracil in patients with 3L mCRC (Table 6).[46]

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 trifluridine-tipiracil were included in the safety set (SS), with patients analysed according to the treatment they received.

**Table 6: Primary and secondary endpoints for the SUNLIGHT trial (time frame: 12 months)**

| | |
|---|---|
| **Primary Endpoint** | OS: Observed time elapsed between the date of randomisation and the date of death due to any cause |
| **Secondary Endpoints** | PFS: Time elapsed between randomisation and the date of radiologic tumour progression according to RECIST v1.1 by investigator's judgement or death from any cause |
| | ORR: Proportion of patients with objective evidence of CR or PR according to RECIST v1.1 and using investigator's tumour assessment |
| | DCR: Proportion of patients with objective evidence of CR or PR or stable disease according to RECIST v1.1 and using investigator's tumour assessment |
| | TEAEs: Assessed by CTCAE v5.0, including SAEs |
| | QoL: Assess patients health and activities using EORTC QLQ-C30 |
| | QoL: Assess patients health and activities using EQ-5D-5L |

**Source**: NCT04737187 (clinicaltrials.gov)

**Key**: CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimension-5 levels; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SAEs, serious adverse events; TEAEs, treatment-related emergent adverse events

### B.2.3.3Summary of trial methodology

**Table 7: Summary of trial methodology (SUNLIGHT)**

| | |
|---|---|
| **Study** | SUNLIGHT[46] |
| **Study design** | open-label, multinational, randomised, controlled two-arm Phase 3 trial |
| **Population** | 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 |
| **Intervention(s)** | Trifluridine-tipiracil + bevacizumab |
| **Comparator(s)** | Trifluridine tipiracil monotherapy |
| **Indicate if study supports application for marketing authorisation** | Yes |
| **Indicate if study used in the economic model** | Yes |
| **Rationale if study not used in model** | N/A |
| **Reported outcomes specified in the decision problem** | OS: Observed time elapsed between the date of randomisation and the date of death due to any cause<br>PFS: Time elapsed between randomisation and the date of radiologic tumour progression according to RECIST v1.1 by investigator's judgement or death from any cause |
| **All other reported outcomes** | ORR: Proportion of patients with objective evidence of CR or PR according to RECIST v1.1 and using investigator's tumour assessment |
| | DCR: Proportion of patients with objective evidence of CR or PR or stable disease according to RECIST v1.1 and using investigator's tumour assessment |
| | TEAEs: Assessed by CTCAE v5.0, including SAEs |
| | QoL: Assess patients health and activities using EORTC QLQ-C30 |
| | QoL: Assess patients health and activities using EQ-5D-5L |

**Key**: CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimension-5 levels; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SAEs, serious adverse events; TEAEs, treatment-related emergent adverse events



### B.2.3.4Baseline characteristics

Between November 2020 and February 2022, 492 patients were enrolled to receive trifluridine-tipiracil plus bevacizumab (n=246) or trifluridine-tipiracil monotherapy (n=246) (FAS population). Demographic and clinical characteristics of patients at baseline were balanced between the two treatment groups and reflected those of the target population (Table 8).[46]

Most patients in the SUNLIGHT trial had cancer of the colon (73% in both cohorts), and the most common metastatic sites were the liver and the lung. Almost all patients had an ECOG PS of 0 or 1 at baseline. Every patient was tested for *RAS*-mutation, with 69% of patients having a *RAS*-mutant tumour. This is higher than that in the general population of patients with mCRC, potentially reflecting preferential referral of patients with *RAS* wild-type tumours to clinical trials of anti-EGFR therapy.[46]

Most patients had received two previous chemotherapy regimens for mCRC, involving fluoropyrimidine, irinotecan, and oxaliplatin for all patients, plus an EGFR monoclonal antibody for *RAS* WT patients. An anti-VEGF monoclonal antibody was optional (except France, where it is mandatory), and most of the patients had received one in prior lines. Most patients (92.1%) had received two previous treatment regimens for metastatic disease; however, 4.5% of the patients in the combination group and 6.1% in the trifluridine-tipiracil monotherapy group had received only one first-line triplet regimen, and 2.6% of the patients in the trial had received three or more previous drug regimens for metastatic disease.[46]

**Table 8: Baseline characteristics for patients in the Phase 3 SUNLIGHT trial**

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| ***Demographics*** | | |
| Gender, n (%) | | |
| Male | 122 (49.6) | 134 (54.5) |
| Female | 124 (50.4) | 112 (45.5) |
| Age, median years (range) | 62 (20; 84) | 64 (24; 90) |
| <65, n (%) | 146 (59.3) | 129 (52.4) |
| ≥65, n (%) | 100 (40.7) | 117 (47.6) |

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| Geographic Region, n (%) | | |
| North America | 8 (3.3) | 8 (3.3) |
| European Union | 158 (64.2) | 157 (63.8) |
| Rest of the World | 80 (32.5) | 81 (32.9) |
| ***ECOG PS, n (%)*** | | |
| 0 | 119 (48.4) | 106 (43.1) |
| 1 | 127 (51.6) | 139 (56.5) |
| 2 | 0 | 1 (0.41)[a] |
| ***Primary site, n (%)*** | | |
| Colon | 180 (73.2) | 181 (73.6) |
| Rectum | 66 (26.8) | 65 (26.4) |
| ***Primary tumour location, n (%)*** | | |
| Right | 62 (25.2) | 77 (31.3) |
| Left | 184 (74.8) | 169 (68.7) |
| ***Number of metastatic organ sites, n (%)*** | | |
| 1-2 | 152 (61.8) | 141 (57.3) |
| ≥3 | 94 (38.2) | 105 (42.7) |
| ***Previous metastatic drug treatment, n (%)*** | | |
| Fluoropyrimidine | 246 (100) | 246 (100) |
| Irinotecan | 246 (100) | 245 (99.6) |
| Oxaliplatin | 241 (98.0) | 243 (98.8) |
| Anti-VEGF | 178 (72.4) | 176 (71.5) |
| Anti-EGFR in *RAS* WT* | 67/71 (94.4) | 66/71 (93.0) |
| ***Number of prior metastatic drug regimens, n (%)*** | | |
| 1 | 11 (4.5) | 15 (6.1) |
| 2 | 229 (93.1) | 224 (91.1) |
| ≥ 3 | 6 (2.4) | 7 (2.8) |
| ***Tumour mutational status, n (%)*** | | |
| *RAS* | | |
| Mutant | 171 (69.5) | 170 (69.1) |
| WT | 75 (30.5) | 76 (30.9) |
| *BRAF* | | |
| Mutant | 8 (3.3) | 11 (4.5) |
| WT | 159 (64.6) | 156 (63.4) |
| Unknown/Missing data | 79 (32.1) | 79 (32.1) |
| MMR/MSI | | |
| MSI/high/MMR deficient | 13 (5.3) | 8 (3.3) |

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| MSS/MSI low/MMR proficient<br>Unknown/Missing data | 139 (56.5)<br>94 (38.2) | 145 (58.9)<br>93 (37.8) |
| ***Site of metastasis, n (%)[b]*** | | |
| Liver | 194 (78.86) | 188 (76.42) |
| Lung | 157 (63.82) | 154 (62.60) |
| Lymph node | 95 (38.62) | 101 (41.06) |
| Peritoneal | 60 (24.39) | 60 (24.39) |
| Soft tissue | 9 (3.66) | 9 (3.66) |
| Bone | 22 (8.94) | 30 (12.20) |
| Brain | 2 (0.81) | 0 |
| Skin | 0 | 1 (0.41) |
| Other | 31 (12.60) | 38 (15.45) |
| ***Prior treatment with bevacizumab, n (%)[b]*** | | |
| No | 68 (27.64) | 70 (28.46) |
| Yes | 178 (72.36) | 176 (71.54) |

**Source**: (Prager 2023b)

**Note**: Data was used until 19 July 2022. Percentages are based on N, except (*) based on the number of patients for whom RAS Status was wild-type. [a]One patient had an ECOG PS rated 2 at baseline prior to treatment while it was rated 1 at inclusion; [b]data from CSR

**Key**: CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable; N/A, not applicable; PS, performance status; SD, standard deviation; VEGF, vascular endothelial growth factor; WT, wild-type

### B.2.3.5Planned subgroup analyses

The Phase 3 SUNLIGHT trial planned for three stratification factors as well as several subgroup analyses (Table 9).

**Table 9: Planned stratification factors and subgroup analyses in the SUNLIGHT trial**

| | |
|---|---|
| **Stratification factors** | *RAS*-mutation status (mutant, wild-type)<br>Time since first metastasis diagnosis (<18 months, ≥18 months)<br>Geographical location (North America, European Union, and Rest of the World) |
| **Pre-planned subgroups** | Age (<65 years, ≥65 years)<br>Location of primary disease (right, left)<br>ECOG PS (0, ≥1)<br>Sex (female, male)<br>Prior surgical resection (yes, no) |

| | |
|---|---|
| | Number of metastatic sites (1-2, ≥3)<br>Neutrophils to lymphocytes ratio (NLR <3, NLR ≥3)<br>Number of prior metastatic drug regimens (1, ≥2)<br>*BRAF* mutation status (mutant, wild-type)<br>MSI status (MSI-H, MSS/MSI-L)<br>Prior bevacizumab (yes, no)<br>Subsequent regorafenib (yes, no) |

**Source:** (Servier 2022)

**Key**: BRAF, v-raf murine sarcoma viral oncogene homolog B1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability low; MSS, microsatellite stable; NLR, neutrophils to lymphocyte ratio; RAS, rat sarcoma

### *B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

The primary objective was to show the superiority of trifluridine-tipiracil plus bevacizumab over trifluridine-tipiracil alone with respect to OS. The trial was designed to have 90% power to detect a hazard ratio of 0.70 (a 30% lower risk of death during the observation period with trifluridine-tipiracil plus bevacizumab than with trifluridine-tipiracil alone), with the use of a log-rank test and a one-sided type I error rate of 0.025. A total of 490 patients (245 in each group) and at least 331 events (death from any cause) were required for the primary analysis. A hierarchical testing strategy was used to control the overall type I error rate; progression-free survival would be evaluated only if the primary analysis showed that overall survival differed significantly between the two trial groups. OS and PFS reflected the duration of survival in all patients, regardless of whether an intercurrent event (defined as the administration of additional anti-cancer therapy, treatment discontinuation, or a switch between trial groups) occurred. 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, and a stratified Cox proportional-hazards model was used to assess the magnitude of the treatment difference.

Subgroup analyses of OS and PFS were pre-specified to assess the homogeneity of the treatment effect across subgroups of patients. An unstratified Cox-regression model

with trial group as a predictor variable was fitted separately for each subgroup category, and the hazard ratio for the assigned treatment, along with the associated 95% confidence interval, was determined. A pre-specified multivariate analysis of overall survival was also performed with the use of a Cox proportional-hazards model; variables were identified for inclusion in a multivariable model by means of stepwise selection on the basis of P-values. Because choosing variables in this fashion can result in omission of important confounders and underestimation of the widths of confidence intervals, an additional multivariable-adjusted analysis of overall survival, including all proposed potential confounders without stepwise variable selection, was performed as an ad hoc analysis. Two-sided 95% Clopper–Pearson confidence intervals were used to describe objective response and disease control in each trial group. A two-sided 95% confidence interval for the between-group difference in these outcomes was provided on the basis of normal approximation. Safety data were summarised with the use of descriptive statistics. The time from randomisation to worsening of the ECOG performance status score from 0 or 1 to 2 or more or death was analysed with the use of the Kaplan–Meier method, and a stratified Cox proportional-hazards model was used to assess the magnitude of treatment difference. The stratification factors used at randomisation were applied to all stratified analyses. For all analyses, the widths of the confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing.

### *B.2.5 Critical appraisal of the relevant clinical effectiveness evidence*

The quality assessment of SUNLIGHT is summarised in Table 10. Quality assessments of the studies identified by the SLR are summarised in Appendix D.

**Table 10: Risk of bias**

| Study/ Reference | Study Trial ID (Study Name) | Interventions | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of reported result | Overall |
|---|---|---|---|---|---|---|---|---|
| SUNLIGHT[46] | NCT04737187 (SUNLIGHT) | Trifluridine/ tipiracil & bevacizumab | | | | | | |

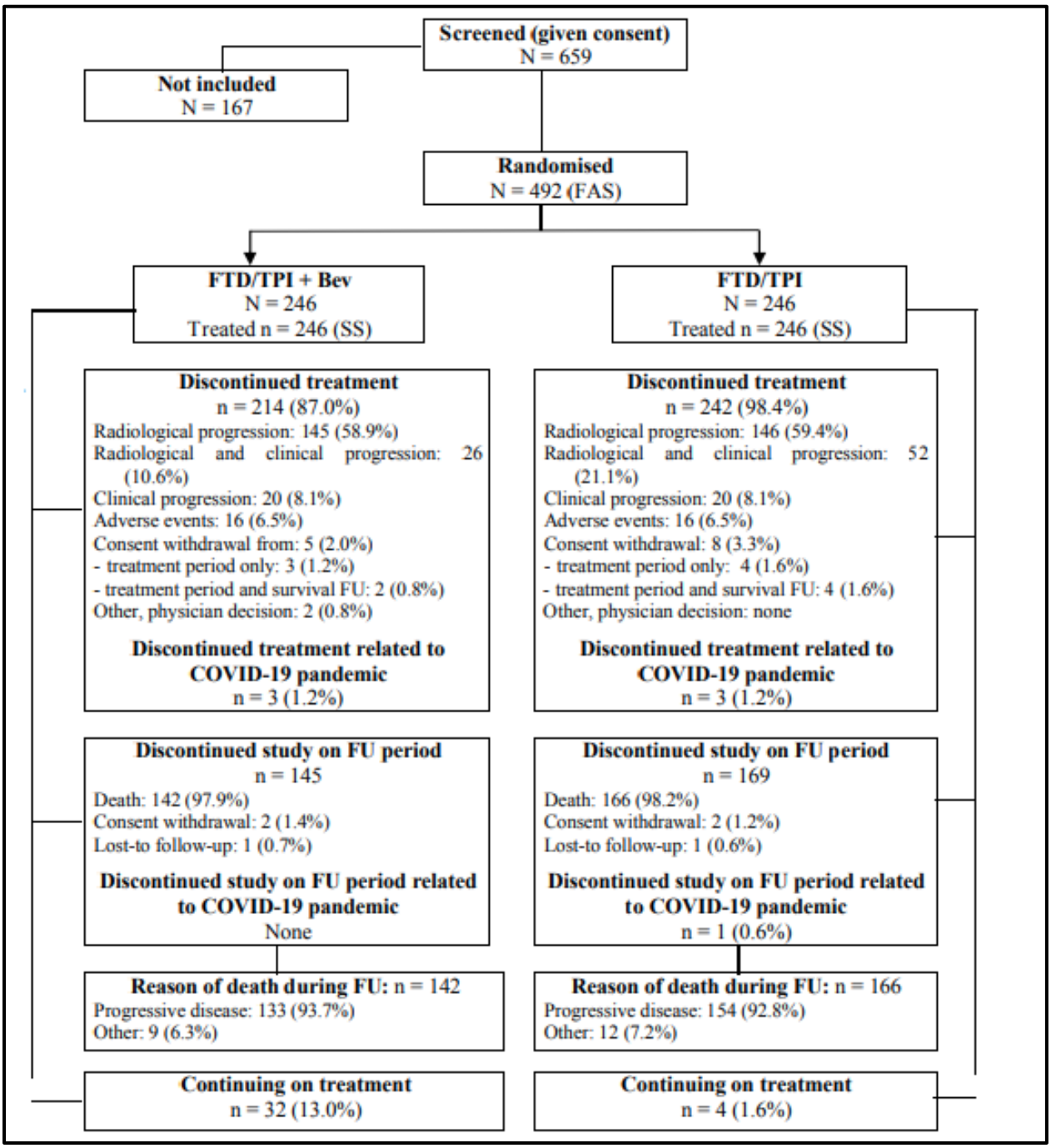
High Unclear Low

## *B.2.6 Clinical effectiveness results of the relevant studies*

### B.2.6.1 Patient disposition

Overall disposition of randomised patients by group in the full analysis set of the SUNLIGHT trial is presented in Figure 7.

**Figure 7: Patient disposition**




**Source**: (Servier 2022)

**Notes**: percentages are based on n

**Key**: Bev, bevacizumab; FAS:,full analysis set; FTD/TPI, trifluridine-tipiracil; FU, follow-up; SS, safety set



### B.2.6.2 Primary Analysis | Overall survival

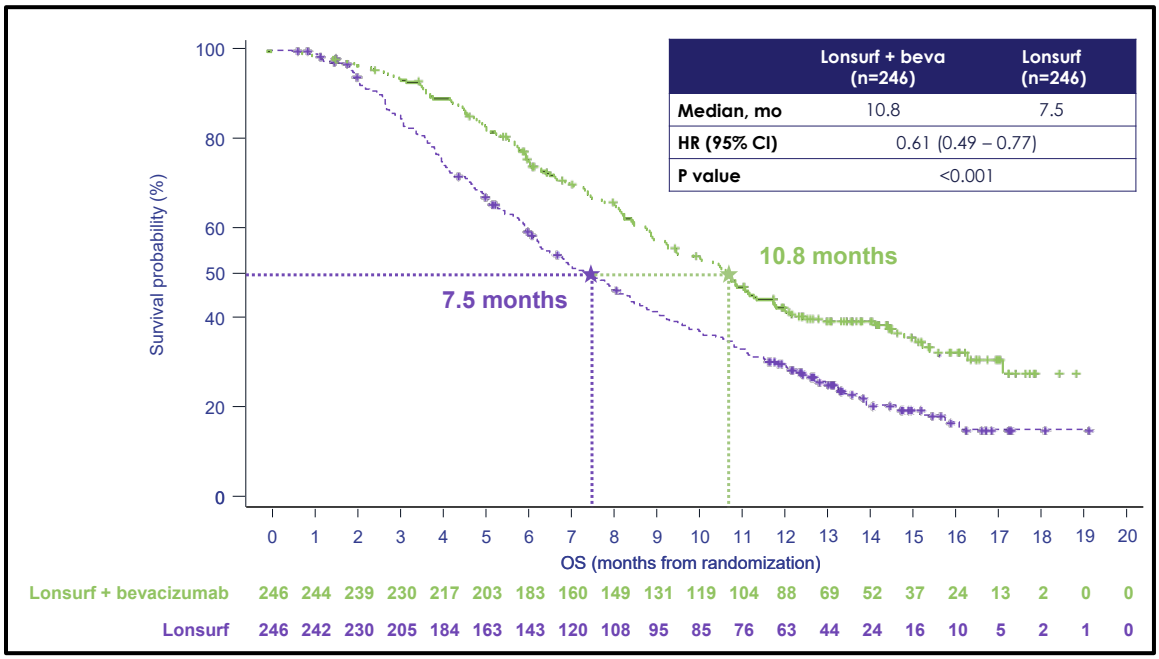
The primary analysis of OS was performed at the survival cut-off of July 19, 2022. As of this survival cut-off, events (deaths) in the FAS were observed for 148 patients (60.2%) in the trifluridine-tipiracil plus bevacizumab group and 183 patients (74.4%) in the trifluridine-tipiracil group.[2]

The median follow-up was 14.2 months (interquartile range: 12.6 to 16.4 months) in the trifluridine-tipiracil plus bevacizumab group and 13.6 months (interquartile range: 12.7 to 15.9 months) in the trifluridine-tipiracil monotherapy group. At the time of the analysis, 13.0% of the patients in the combination group and 1.6% of the patients in the trifluridine-tipiracil monotherapy group were still receiving treatment.[46]

The combination of trifluridine-tipiracil plus bevacizumab resulted in a clinically meaningful and statistically significant survival benefit compared to trifluridine-tipiracil monotherapy (Figure 8). Trifluridine-tipiracil plus bevacizumab improved OS by 3.3 months compared to trifluridine-tipiracil monotherapy (median OS of 10.8 months [95% CI: 9.4, 11.8] with trifluridine-tipiracil plus bevacizumab vs. 7.5 months [95% CI: 6.3, 8.6] with trifluridine-tipiracil monotherapy).

**Figure 8: Kaplan-Meier curve for OS in patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023b)[46]

**Notes:** Primary analysis of OS was performed on survival data on 19 July 2022, using FAS of 492 patients with mCRC

**Key**: 3L, third-line; beva, bevacizumab; CI, confidence interval FAS, full analysis set; HR, hazard ratio; Lonsurf; trifluridine-tipiracil; mCRC, metastatic colorectal cancer; mo, months; OS, overall survival

The improvement in median OS with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy resulted in a HR of 0.61 (95% CI: 0.49, 0.77; p<0.001) , corresponding to 39% relative reduction in the relative risk of death. The estimate of survival probability was consistently higher with trifluridine-tipiracil plus bevacizumab than with trifluridine-tipiracil monotherapy at 6 months, 12 months, and 18 months (Table 11).

**Table 11: Median OS and survival probability for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**

| | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** |
|---|---|---|
| OS, median months[1] (95% CI)[2] | 10.78 (9.36, 11.83) | 7.46 (6.34, 8.57) |



| | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| Hazard ratio* (95% CI) | 0.61 (0.49, 0.77) | |
| p-value[3] | p<0.001 | |
| ***Survival probability*** | | |
| Survival probability at 6 months[1] (95% CI)[4] | 77% (72%, 82%) | 61% (55%, 67%) |
| Survival probability at 12 months[1] (95% CI)[4] | 43% (36%, 49%) | 30% (24%, 36%) |
| Survival probability at 18 months[1] (95% CI)[4] | 28% (19%, 37%) | 15% (9%, 22%) |

**Source**: (Servier 2022, Prager 2023b) CSR page 70

**Notes**: Median OS, HR, and survival probability was performed on survival data that reported through the data of 19 July 2022 from the SUNLIGHT trial. mCRC patients received either trifluridine-tipiracil + bevacizumab (n=246) or trifluridine-tipiracil monotherapy (n=246). 1. Kaplan-Meier estimate; 2. Methodology of Brookmeyer and Crowley; 3. Stratified Log-Rank Test at one-sided 2.5% level of significance (IWRS stratification factors: geographic region, time since first metastasis diagnosis, *RAS* status); 4. Using log-log transformation methodology of Kalbfleisch and Prentice; * Stratified Cox proportional hazard model using IWRS stratification factors

**Key**: 3L, third-line; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; IWRS, Interactive Web Response System; mCRC, metastatic colorectal cancer; OS, overall survival; RAS, rat sarcoma

### B.2.6.3 Key secondary analysis

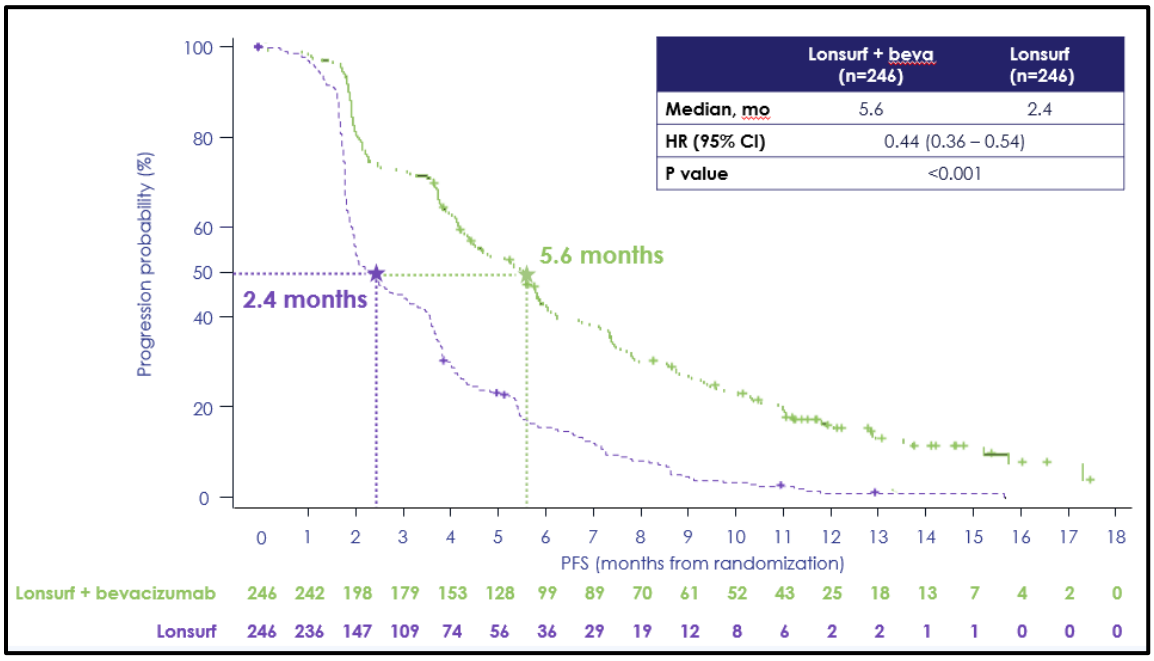
#### *B.2.6.3.1 Progression-free survival*

Trifluridine-tipiracil plus bevacizumab resulted in a clinically and statistically significant improvement in PFS compared to trifluridine-tipiracil 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 (Figure 9).

Trifluridine-tipiracil + bevacizumab resulted in an increase of 3.2 months median PFS, a greater than two-fold increase versus trifluridine-tipiracil monotherapy (5.6 months [95% CI: 4.5, 5.9] vs. 2.4 months [95% CI: 2.1, 3.2]; Table 12). The probability of being progression-free was consistently higher in patients receiving trifluridine-tipiracil plus bevacizumab than in patients receiving trifluridine-tipiracil monotherapy at 3 months, 6 months, 9 months, and 12 months (Table 12).

**Figure 9: Kaplan-Meier curve for PFS for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023b)[46]

**Notes**: PFS was performed based on survival data from the SUNLIGHT trial on mCRC patients reported up to 19 July 2022. Patients received either trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy.

**Key**: 3L, third-line; beva, bevacizumab; FAS, full analysis set; Lonsurf; trifluridine-tipiracil; mCRC, metastatic colorectal cancer; PFS, progression-free survival

**Table 12: Full PFS data for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**

| | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** |
|---|---|---|
| PFS (median months)[1] (95% CI)[2] | 5.55 (4.50, 5.88) | 2.40 (2.07, 3.22) |
| Hazard ratio* (95% CI) | 0.44 (0.36, 0.54) | |
| p-value[3] | p<0.001 | |
| ***PFS probability*** | | |
| Survival probability at 3 months[1] (95% CI)[4] | 73% (67%, 78%) | 45% (39%, 51%) |
| Survival probability at 6 months[1] (95% CI)[4] | 43% (37%, 49%) | 16% (11%, 21%) |
| Survival probability at 9 months[1] (95% CI)[4] | 28% (22%, 34%) | 5% (3%, 9%) |
| Survival probability at 12 months[1] (95% CI)[4] | 16% (12%, 21%) | 1% (0%, 3%) |

**Source**: (Servier 2022, Prager 2023b) CSR page 77



**Notes**: PFS analysis was performed on data that was date locked on 19 July 2022. 1. Kaplan-Meier estimates; 2. Methodology of Brookmeyer and Crowley; 3. Stratified Log-Rank Test at one-sided 2.5% level of significance (IWRS stratification factors: geographic region, time since first metastasis diagnosis, *RAS* status); 4. Using log-log transformation methodology of Kalbfleisch and Prentice; * Stratified Cox proportional hazard model using IWRS stratification factors

**Key**: 3L, third-line; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IWRS, interactive web response system; mCRC, metastatic colorectal cancer; PFS, progression-free survival; RAS, rat sarcoma

#### *B.2.6.3.2 Overall response rate*

The clinical data cut-off for non-survival data was July 5, 2022. ORR was significantly higher for patients receiving trifluridine-tipiracil plus bevacizumab (6.1% [95% CI: 3.5%, 9.9%]) compared with trifluridine-tipiracil monotherapy (1.2% [95% CI: 0.3%, 3.5%]; Table 13)[46] 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.

DCR was also significantly higher in patients treated with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy: 69.5% of patients receiving trifluridine-tipiracil plus bevacizumab had their disease controlled compared with 41.9% receiving trifluridine-tipiracil (Table 13). The between-group difference in DCR was 27.6% (95% CI: 19.21, 36.07; p<0.001) (Servier 2022, Prager 2023b).

**Table 13: Summary of tumour response for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**

| Tumour Response | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| CR, n (%) | 0 (-) | 1 (0.4) |
| PR, n (%) | 15 (6.1) | 2 (0.81) |
| Stable disease, n (%) | 156 (63.41) | 100 (40.65) |
| ORR, n (%) | 15 (6.10) | 3 (1.22) |
| DCR, n (%) | 171 (69.51) | 103 (41.87) |

**Source**: (Servier 2022, Prager 2023b) CSR page 82

**Note**: Responses recorded after intercurrent event (e.g. additional anti-cancer treatment or treatment arm switch) were excluded to align with the “while on treatment” strategy

**Key**: 3L, third-line; CR, complete response; CSR, clinical study report; DCR, disease control rate; FAS, full analysis set; mCRC, metastatic colorectal cancer; ORR, overall response rate; PR, partial response

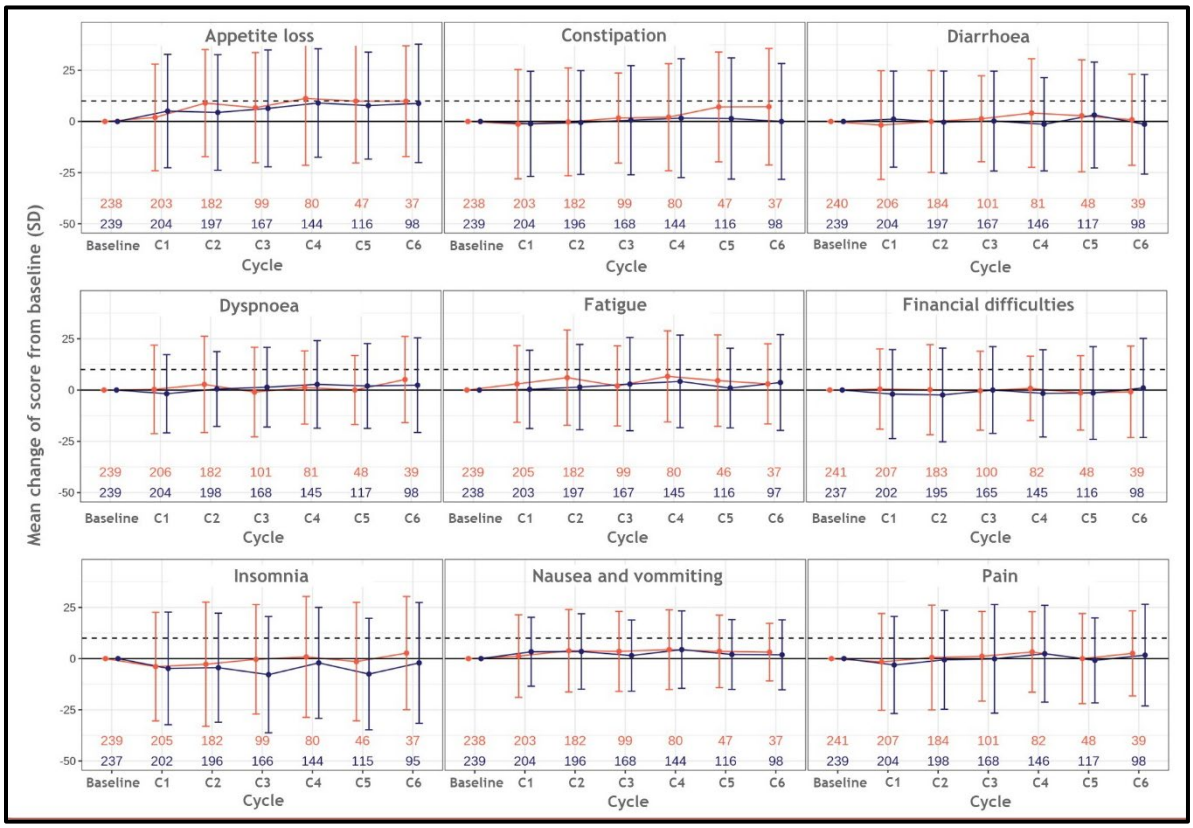
#### *B.2.6.3.3 Patient reported outcomes*

Data were collected from the EORTC QLQ-C30 questionnaire (a cancer-specific QoL measure composed of functional, physical, and global health status [GHS] subscales) and the EuroQol EQ-5D-5L questionnaire (a more general QoL measure, assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and patient's self-rated health [visual analogue score/VAS]). HRQoL was evaluated at baseline, at each cycle, and at the withdrawal visit. HRQoL outcomes analyses included change from baseline and time until definitive deterioration of ≥10 points in GHS and sub-scale scores for the QLQ-C30, and change from baseline in VAS and health utility index for the EQ-5D-5L[46]. Among the 492 randomised patients, >97.6% had QoL data at baseline in the trifluridine-tipiracil plus bevacizumab (n=239) and trifluridine-tipiracil monotherapy (n=241) arms.[46]

Cancer-related (QLQ-C30) and general (EQ-5D-5L) HRQoL were maintained for the two patient groups from baseline to Cycle 6, and no clinically relevant changes in mean scores were observed in any of the sub-domains. Therefore, patients treated with both trifluridine-tipiracil plus bevacizumab and with trifluridine-tipiracil monotherapy did not show increased symptom burden over time, as assessed by the QLQ-C30 symptom domains (Figure 10). Similarly, patients were able to maintain functioning across physical, cognitive, and social sub-domains with both treatments, with no decline over time observed in either group (Figure 11). Similar maintenance over time was observed for general QoL as measured by the EQ-5D-5L (Figure 12).

**Figure 10: Cancer-specific physical symptom sub-domains QoL scores (EORTC QLQ-C30) from Baseline to Cycle 6 (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023a)[46]

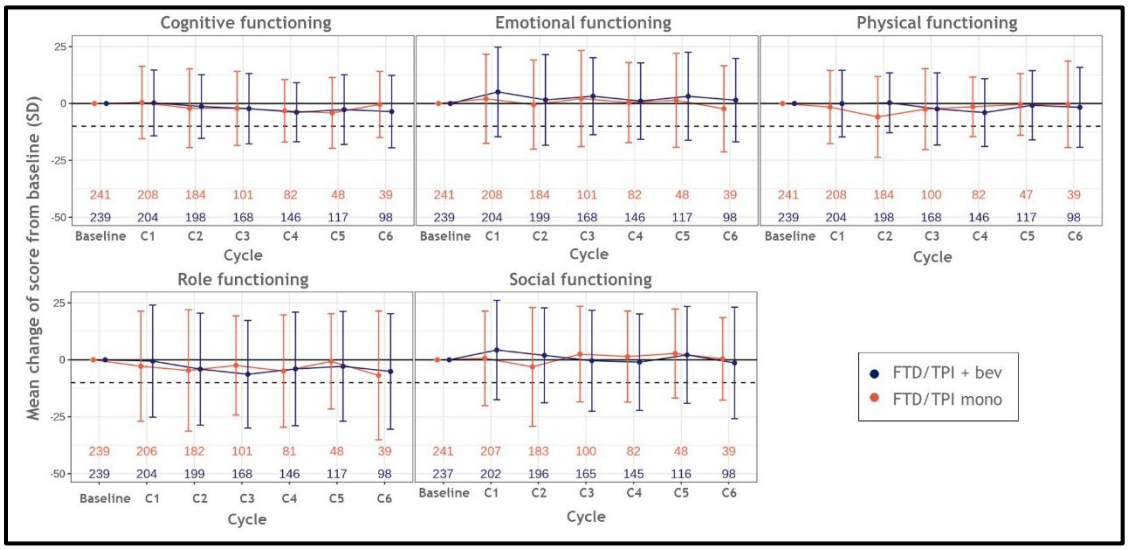
**Notes**: Blue: trifluridine-tipiracil + bevacizumab (n=239), Red: trifluridine-tipiracil monotherapy (n=241). QoL for the first 6 cycles are presented, as questionnaire completion rates dropped to less than 10% after this time-point, making it difficult to evaluate the results

**Key**: C, cycle; EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; QoL, quality of life; SD, standard deviation



**Figure 11: Cancer-specific functioning sub-domains QoL scores (EORTC QLQ-C30) from Baseline to Cycle 6 (SUNLIGHT trial, n=492 [FAS])**

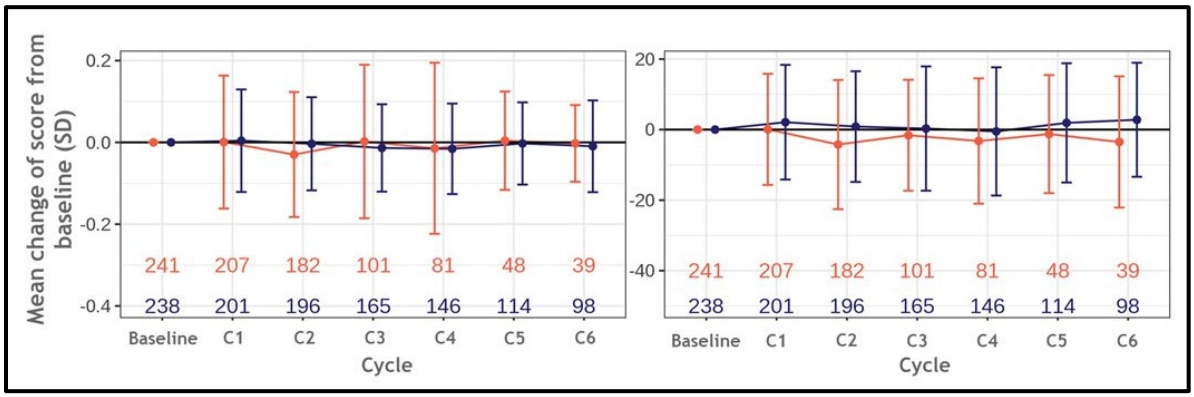



**Source**: (Prager 2023a)

**Notes**: Blue: trifluridine-tipiracil + bevacizumab (n=239), Red: trifluridine-tipiracil monotherapy (n=241). QoL for the first 6 cycles are presented, as questionnaire completion rates dropped to less than 10% after this time-point, making it difficult to evaluate the results

**Key**: bev, bevacizumab; C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; FTD/TP,: trifluridine-tipiracil; mono, monotherapy; QoL, quality of life; SD, standard deviation

**Figure 12: General QoL scores (EQ-5D-5L) from Baseline to Cycle 6 – index utility score (left) and VAS (right) (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023a)

**Notes**: Blue: trifluridine-tipiracil + bevacizumab (n=239), Red: trifluridine-tipiracil monotherapy (n=241). QoL for the first 6 cycles are presented, as questionnaire completion rates dropped to less than 10% after this time-point, making it difficult to evaluate the results

**Key**: C, cycle; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FAS, full analysis set; FTD/TPI, trifluridine-tipiracil; QoL, quality of life; SD, standard deviation; VAS, visual analogue scale



The percentage of patients with definitive EORTC QLQ-C30 GHS deterioration of >10 points (where a >10-point change is considered a clinically meaningful difference) was lower in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil monotherapy group: 48.8% vs. 57.3%. In contrast, the proportion of patients who worsened <10 points from baseline in EORTC QLQ-C30 GHS (considered a non-clinically meaningful difference) was similar in the two groups: 61.2% in the trifluridine-tipiracil + bevacizumab group and 57.3% in the trifluridine-tipiracil monotherapy group[2,46]

**Table 14: EORTC QLQ-C30 GHS deterioration in patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**

| | **Trifluridine-tipiracil + bevacizumab (n = 246)** | **Trifluridine-tipiracil (n = 246)** |
|---|---|---|
| Number of censors, n (%) | 126 (51.22) | 105 (42.68) |
| Number of censors due to new anti-cancer therapy, n (%) | 83 (33.74) | 89 (36.18) |
| Number of events, n (%) | 120 (48.78) | 141 (57.32) |
| ≥10 points definitive deterioration | 62 (25.20) | 72 (29.27) |
| Death | 58 (23.58) | 69 (28.05) |

**Source:** (Servier 2022, Prager 2023a) CSR table: (11.3.2.1)[1]

**Notes:** Death was considered as definitive deterioration of QoL Percentages are based on N. Number of censors refers to the number of patients who did not experience definitive deterioration of 10 points in global health status during the study but whose follow-up time ended before the study was completed. New anti-cancer therapy refers to the number of patients who received a new treatment for their cancer during the study, either because their disease progressed or because they developed new lesions. These patients were censored at the time they started the new treatment because their GHS score after that point could no longer be considered a reliable measure of the effect of the original treatment

**Key**: 3L, third-line; CSR, clinical study report; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; GHS, Global health status; mCRC, metastatic colorectal cancer

The time until definitive deterioration in EORTC QLQ-C30 GHS (defined as the time from randomisation to the first deterioration in HRQoL score ≥10 points compared to baseline, with no later improvement above this threshold) was statistically longer in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil group ($p<0.001$, stratified log-rank test), with median values of 8.5 months vs. 4.7 months,

respectively (HR: 0.50 [95% CI: 0.38, 0.65]; Table 15). This difference translates to a median 3.8-month delay in definitive deterioration in HRQoL compared with trifluridine-tipiracil monotherapy. This reduction in risk of definitive worsening with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy was observed in all scales and subscales (Figure 13)[46]

**Table 15: Time until definitive EORTC QLQ-C30 GHS deterioration for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS])**

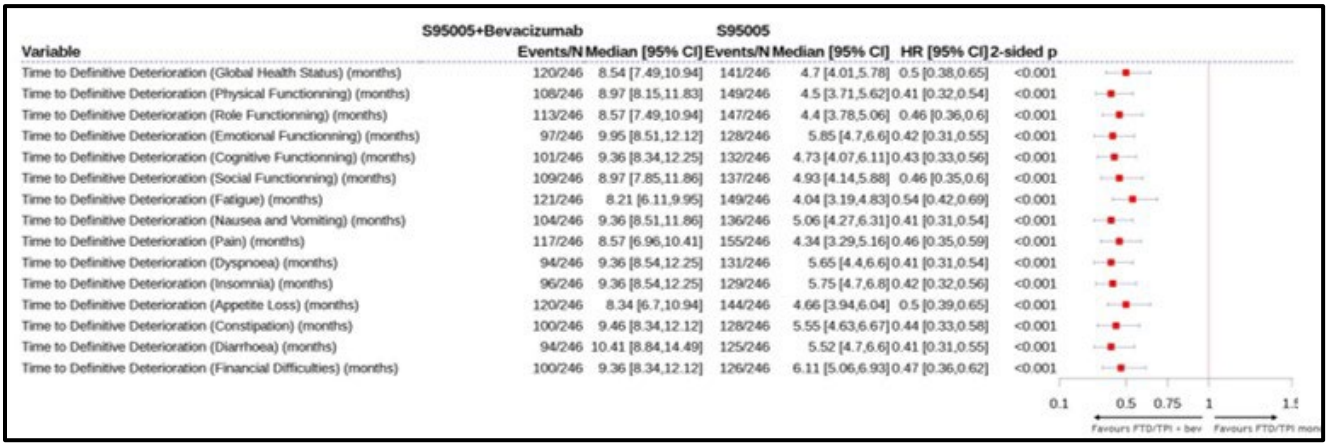
| Time until definitive deterioration in GHS | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| Median (months)[1] | 8.54 | 4.70 |
| 95% CI[2] | [7.49; 10.94] | [4.01; 5.78] |
| Min; Max | 0.07; 17.58 | 0.03; 14.32 |
| P-value[3] | <0.001 | |

**Source:** (Servier 2022, Prager 2023a) CSR table: (11.3.2.1) 1

**Notes:** Time until definitive deterioration was defined as the time from randomisation to the first deterioration in QoL score ≥10 points compared to baseline with no later improvement above this threshold. Death was considered as definitive deterioration of QoL Percentages are based on N. 1. Kaplan-Meier estimates. 2. Methodology of Brookmeyer and Crowley. 3. Stratified Log-Rank Test (IWRS stratification factors: geographic region, time since first metastasis diagnosis, RAS status)

**Key**: 3L, third-line; CI, confidence interval; CSR, clinical study report; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; GHS, Global health status; IWRS, Interactive Web Response System; max, maximum; mCRC, metastatic colorectal cancer; min, minimum

**Figure 13: Risk of definitive deterioration ≥10 points in EORTC QLQ-C30 with trifluridine-tipiracil + bevacizumab vs. trifluridine-tipiracil monotherapy (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023a)



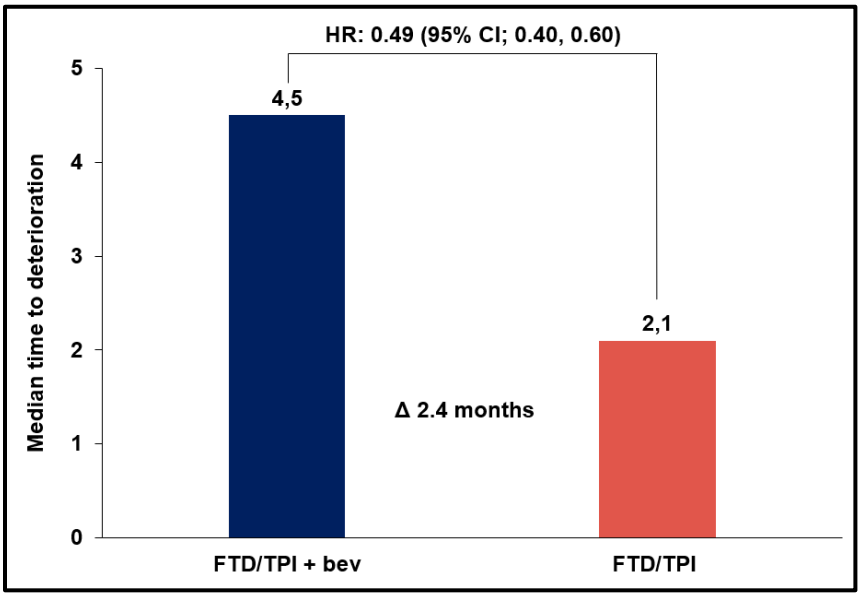
 

**Notes**: Blue: trifluridine-tipiracil + bevacizumab (n=239), Red: trifluridine-tipiracil monotherapy (n=241). QoL for the first 6 cycles are presented, as questionnaire completion rates dropped to less than 10% after this time-point, making it difficult to evaluate the results

**Key**: bev, bevacizumab; C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; FTD/TPI, trifluridine-tipiracil ; QoL, quality of life; SD, standard deviation

In a sensitivity analysis considering disease progression and death as a definitive deterioration measured by QLQ-C30, HRQoL deteriorated significantly later: median time to deterioration in the trifluridine-tipiracil plus bevacizumab arm was 4.5 months vs. 2.07 months in the trifluridine-tipiracil monotherapy arm (HR: 0.49; 95% CI; 0.40, 0.60), consistently favouring the trifluridine-tipiracil plus bevacizumab arm (Figure 14). A similar result was observed with the EQ-5D-5L utility score and VAS, showing that HRQoL deteriorated later in patients receiving trifluridine-tipiracil plus bevacizumab compared to patients receiving trifluridine-tipiracil monotherapy[46]

**Figure 14: EORTC QLQ-C30 GHS sensitivity analysis: time to definitive deterioration by ≥10 points with disease progression and death considered as events (SUNLIGHT trial, n=492 [FAS])**




**Source**: (Prager 2023a)

**Key**: bev, bevacizumab; CI, confidence interval; EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–- Core 30; FAS, full analysis set; FTD/TPI, trifluridine-tipiracil; GHS, global health status; HR, hazard ratio

In the FAS, the trifluridine-tipiracil plus bevacizumab group showed a statistically significant improvement in time to worsening of ECOG PS to ≥2 compared to the

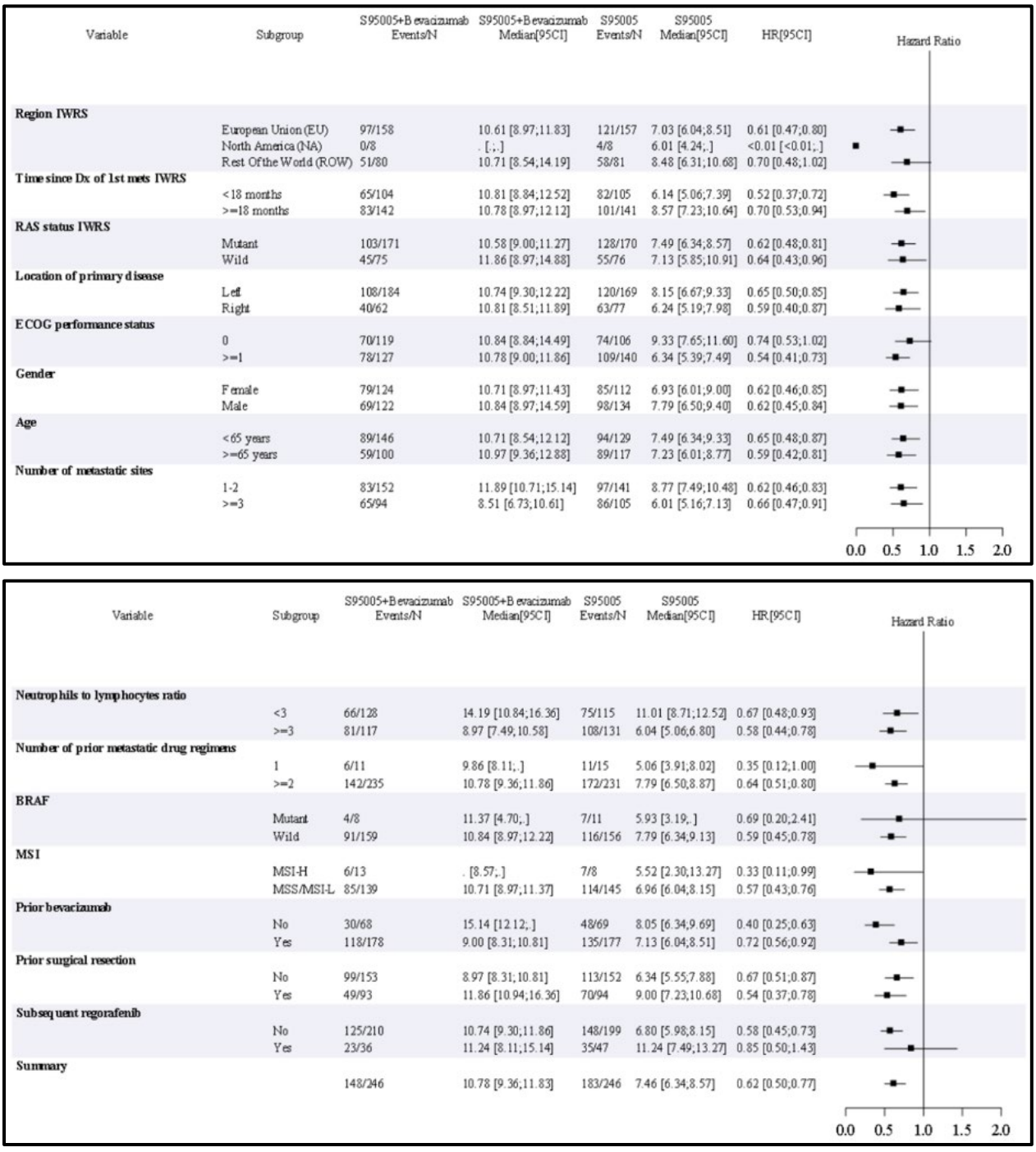
trifluridine-tipiracil group (p<0.001, stratified log-rank test). The median time to worsening of ECOG PS to ≥2 was 9.3 months (95% CI: 8.34, 10.61) with trifluridine-tipiracil plus bevacizumab, compared to 6.3 months (95% CI: 5.55, 7.23) with trifluridine-tipiracil monotherapy (HR: 0.54 [95% CI: 0.43, 0.67], p<0.001) . This difference translates to a median increase in time to worsening to an ECOG PS ≥2 of 3 months.

### *B.2.7 Subgroup analysis*

At the survival data cut-off (July 19, 2022), trifluridine-tipiracil plus bevacizumab provided consistent survival benefits for patients with 3L mCRC compared with trifluridine-tipiracil across all pre-specified subgroups (Figure 15). Overall, the subgroup analysis demonstrated that trifluridine-tipiracil plus bevacizumab was effective regardless of the stratification factors of age, time since first metastasis diagnosis, or *RAS* status, and regardless of other pre-specified factors such as ECOG PS, number of metastatic sites, or prior bevacizumab use. The HRs were consistently in favour of trifluridine-tipiracil plus bevacizumab in all 15 subgroups examined, and the effect was statistically and clinically significant regardless of prior exposure to bevacizumab.[2,46]

**Figure 15: Forest plot of hazard ratios for treatment effect on primary OS by selected subgroup (FAS; N=492)**




**Source**: (Servier 2022)

**Key**: BRAF, BRAF gene; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; IWRS, interactive Web Response System; mets, metastasis; MSI, microsatellite instability; MSI-H, high-level microsatellite instability; MSI-L, low-level microsatellite



Overall, the clinicians considered the SUNLIGHT trial generalisable to clinical practice despite this difference. Despite this, in the SUNLIGHT trial, the majority of patients had received prior bevacizumab treatment (72.2%) which differs from the patients who would receive treatment at 3L in UK clinical practice. Prior bevacizumab use was not a stratification factor in the SUNLIGHT study. Therefore, the company wishes for the whole population to be considered but felt it important to get clinician feedback on their views as to whether prior bevacizumab is considered a prognostic factor in patients with mCRC. Feedback to the company indicated that according to the subgroup data, those with no prior bevacizumab would likely achieve a better response, and as such, it was considered that the outcomes from the SUNLIGHT study would be underestimating the effects of trifluridine-tipiracil plus bevacizumab in the UK population by looking at the ITT population from the study. In addition, feedback to the company was that NHS England are looking at a review of bevacizumab in prior lines. Therefore, consensus was that Servier are right to base this on the ITT population and the value in UK patients, at present, may be underestimated.[4]

### *B.2.8 Meta-analysis*

Not applicable.

### *B.2.9 Indirect and mixed treatment comparisons*

Following the SLR (see Section B.2.1), networks of evidence for OS and PFS were constructed for 15 connected RCTs evaluating trifluridine-tipiracil plus bevacizumab or other interventions of interest. Given not all the treatments in the network meta-analysis (NMA) are relevant for the UK decision problem, this section focuses on the 7 trials linking up the relevant comparators for the UK. Details of the other trials and results can be found in a separate report. (Appendix D).

#### B.2.9.1 Method

The objective of the NMA was to estimate the relative treatment effects of trifluridine-tipiracil plus bevacizumab versus other interventions for patients undergoing third-line treatment for refractory mCRC. Where results of the RCTs identified in the SLR formed part of one evidence network and were deemed sufficiently similar for each population of interest, they were synthesized by means of NMAs for OS and PFS. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effects of each intervention compared to a reference treatment. Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained.

An NMA can be conducted with either fixed-effect or random-effects models. In general, the assumptions of random-effects models are preferred as they are expected to be more plausible than fixed-effect models but a sufficient number of studies is not always available to estimate between study heterogeneity. As such, both fixed-effect and random-effects models were considered.

NMAs of reported HRs in terms of OS and PFS assuming proportional hazards between treatments were performed using regression models with a contrast-based normal likelihood for the log HR (and corresponding standard error) for each trial in the network. According to Dias et al[48]., normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

All analyses were performed using R version 4.2.2 (http://www.r-project.org/) and JAGS version 4.3.1 (OpenBUGS Project Management Group).

#### B.2.9.2 Overview of feasibility assessment

A key assumption of the NMA 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. First, the network geometry formed by the RCTs identified in the SLR was evaluated. Of the 26 RCTs identified in the SLR, seven evaluated at least two treatment arms of interest for this decision problem. Thus,

the feasibility assessment described below focuses on the study designs, populations, and outcome availability/definitions of these seven connected trials to evaluate the feasibility of conducting a credible NMA.

#### *B.2.9.2.1 Trial characteristics*

Regarding general trial characteristics, five trials were phase III, and two trials were phase II. One trial was quadruple-blind, one was triple-blind, three were double-blind, and two were open-label. Three trials were multinational, whereas two trials were conducted across the Asia continent or within single countries. The largest trial, RECOURSE, enrolled a total of 800 patients, whereas the smallest trial, Pfeiffer, enrolled a total of 93 patients. The oldest trial, started in 2009, whereas the newest trial, SUNLIGHT, started in 2020.

**Table 16: General trial characteristics**

| Trial ID | Phase | Arms | Study start | Study completion | Masking | Region/ country | N |
|---|---|---|---|---|---|---|---|
| CONCUR[49] | III | Regorafenib<br>Placebo | 2012 | 2016 | Triple-blind | Asia | 136 |
| CORRECT[50] | III | Regorafenib<br>Placebo<br>Cetuximab + irinotecan | 2010 | 2014 | Quadruple-blind | Multinational | 760 |
| Pfieffer 2020[51] | II | FTD/TPI<br>FTD/TPI + bevacizumab | 2017[a] | 2018[a] | Open-label | Denmark | 93 |
| RECOURSE[52] | III | FTD/TPI<br>Placebo | 2012 | 2016 | Double-blind | Multinational | 800 |
| SUNLIGHT[46] | III | FTD/TPI + bevacizumab<br>FTD/TPI | 2020 | 2022 | Open-label | Multinational | 492 |
| TERRA[53] | III | FTD/TPI<br>Placebo<br>Placebo + BSC | 2013 | 2016 | Double-blind | Asia | 406 |
| Yoshino 2012[54] | II | FTD/TPI<br>Placebo | 2009 | 2010 | Double-blind | Japan | 169 |

[a]First/last day of patient enrolment

**Key:** BSC, best supportive care; FTD/TPI, trifluridine/tipiracil

#### *B.2.9.2.2 Trial eligibility criteria*

Regarding trial eligibility criteria, most trials restricted enrolment to patients with an ECOG performance status (or equivalent) of 0 or 1, although Yoshino 2012[54] allowed the enrolment of patients with a performance status of 2 (Table 17). There was heterogeneity among trials in eligibility criteria concerning the number of prior lines of treatment and the treatment regimens previously received for advanced/metastatic disease.

**Table 17: Trial eligibility criteria**

| Trial ID | Age (y) | Disease classification | ECOG PS | Tumor histology | No. of prior treatment lines | Prior treatment regimens for advanced/ metastatic disease |
|---|---|---|---|---|---|---|
| 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 |
| 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 and/or anti-EGFR monoclonal antibody |

| Trial ID | Age (y) | Disease classification | ECOG PS | Tumor histology | No. of prior treatment lines | Prior treatment regimens for advanced/ metastatic disease |
|---|---|---|---|---|---|---|
| TERRA | ≥18 | Metastatic | 0-1 | Adenocarcinoma | ≥2 | Fluoropyrimidine, irinotecan, and oxaliplatin |
| Yoshino 2012 | ≥20 | Metastatic | 0-2 | Adenocarcinoma | ≥2 | Standard chemotherapies |

[a]World Health Organisation performance scale.

**Key:** ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; PS, performance status; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; VEGF, vascular endothelial growth factor; WT, wild-type; y, years.

#### *B.2.9.2.3 Treatment characteristics*

Regarding trials evaluating trifluridine-tipiracil-containing treatment regimens, Pfieffer 2020, RECOURSE, SUNLIGHT, TERRA, used similar trifluridine-tipiracil delivery schedules (i.e., on D1-D5 and D8-12 or D8-14), whereas Yoshino 2012 did not specify the days of trifluridine-tipiracil delivery (Table 18). The doses and delivery schedules for bevacizumab -containing regimens were similar across trials.

**Table 18: Treatment characteristics**

| Trial ID | Arms | Agent 1 | Agent 2 |
|---|---|---|---|
| CONCUR | Regorafenib | Regorafenib, PO (160mg, D1-21, cycle: 4 w, UDP) | -- |
| | Placebo | Placebo, PO (D1-21, cycle: 4 w, UDP) | -- |
| CORRECT | Regorafenib | Regorafenib, PO (160mg, D1-21, cycle: 4 w, UDP) | -- |
| | Placebo | Placebo, PO (D1-21, cycle: 4 w, UDP) | -- |
| Pfieffer 2020 | FTD/TPI | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-12, cycle: 4 w, UDP) | -- |
| | FTD/TPI + bevacizumab | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-12, cycle: 4 w, UDP) | Bevacizumab, IV (5mg/kg, D1 and D15, cycle: 4 w, UDP) |
| RECOURSE | FTD/TPI | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-14, cycle: 4 w, UDP) | -- |
| | Placebo | Placebo, PO (BID, D1-5 and D8-14, cycle: 4 w, UDP) | -- |

| Trial ID | Arms | Agent 1 | Agent 2 |
|---|---|---|---|
| SUNLIGHT | FTD/TPI + bevacizumab | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-12, cycle: 4 w, UDP) | Bevacizumab, IV (5mg/kg, D1 and D15, cycle: 4 w, UDP) |
| | FTD/TPI | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-12, cycle: 4 w, UDP) | -- |
| TERRA | FTD/TPI | FTD/TPI, PO (35mg/m$^2$, BID, D1-5 and D8-12, cycle: 4 w, UDP) | -- |
| | Placebo | Placebo, PO (BID, D1-5 and D8-12, cycle: 4 w, UDP) | -- |
| Yoshino 2012 | FTD/TPI | FTD/TPI, PO (35mg/m$^2$, BID, cycle: 4 w, UDP) | -- |
| | Placebo | Placebo, PO (BID, cycle: 4 w, UDP) | -- |

**Key:** BID, twice daily; BSC, best supportive care; d, day; FTD/TPI, trifluridine/tipiracil; IV, intravenous; PO, oral; UDP, until disease progression; w, week.

#### *B.2.9.2.4 Patient characteristics*

Patient age, sex, race/ethnicity, ECOG performance status, number of prior lines of therapy, and prior bevacizumab or anti-vascular endothelial growth factor (VEGF) therapy were investigated as potential treatment effect modifiers based on a brief review of subgroup results from key trials included in the SLR, current treatment guidelines[55,56], and a previous meta-analysis.[57]

Median patient age and the proportion of male patients were similar across trials (Table 19). The distribution of patient race/ethnicity varied among trials, particularly the proportions of patients who were White or Asian. However, similar OS and PFS reported for ethnicity or geographical region subgroups in CORRECT and RECOURSE imply that White vs. Asian ethnicity is not a treatment effect modifier for this population.

**Table 19: Patient age, sex, race/ethnicity, and performance status**

| Trial ID | Arm | Median age, years (range) | Males, % | Race/ethnicity | | | ECOG performance status | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | White, % | Black, % | Asian, % | 0, % | 1, % | 2, % |
| CONCUR | Regorafenib | 57.5 (50-66)[a] | 62 | 0[b] | 0[b] | 100[b] | 26 | 74 | 0 |

| Trial ID | Arm | Median age, years (range) | Males, % | Race/ethnicity | | | ECOG performance status | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | White, % | Black, % | Asian, % | 0, % | 1, % | 2, % |
| | Placebo | 55.5 (48.5-62)[a] | 49 | 0[b] | 0[b] | 100[b] | 22 | 78 | 0 |
| CORRECT | Regorafenib | 61 (54-67)[a] | 62 | 78 | 1 | 15 | 52 | 48 | 0 |
| | Placebo | 61 (54-68)[a] | 60 | 79 | 3 | 14 | 57 | 43 | 0 |
| Pfieffer 2020 | FTD/TPI | 67 (58-72)[a] | 64 | -- | -- | -- | 32 | 68 | 0 |
| | FTD/TPI + bevacizumab | 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 + bevacizumab | 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 |
| 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; [c]All patients had a performance status of 0-1 according to eligibility criteria.

**Key:** BSC, best supportive care; FTD/TPI, trifluridine/tipiracil.

#### *B.2.9.2.5 Treatment lines*

Trials varied in terms of the number of prior lines of therapy that patients received for advanced/metastatic disease (Table 20).

**Table 20: Number of prior lines of therapy**

| Trial ID | Arm | Number of prior lines of therapy for advanced/metastatic disease | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1, % | ≥1, % | 1-2, % | 2, % | ≥2, % | 2-3, % | 3, % | ≥3, % | >3, % | 4, % | ≥4, % |
| CONCUR | Regorafenib | -- | -- | 35 | -- | -- | -- | 24 | -- | -- | -- | 38 |
| | Placebo | -- | -- | 35 | -- | -- | -- | 25 | -- | -- | -- | 40 |
| CORRECT | Regorafenib | -- | -- | 27 | -- | -- | -- | 25 | -- | -- | -- | 49 |
| | Placebo | -- | -- | 25 | -- | -- | -- | 28 | -- | -- | -- | 47 |
| Pfieffer 2020 | FTD/TPI | -- | -- | 46 | -- | -- | -- | 26 | -- | -- | 17 | 11 |
| | FTD/TPI + bevacizumab | -- | -- | 42 | -- | -- | -- | 28 | -- | -- | 17 | 13 |
| RECOURSE | FTD/TPI | -- | -- | -- | 18 | -- | -- | 22 | -- | -- | -- | 60 |
| | Placebo | -- | -- | -- | 17 | -- | -- | 20 | -- | -- | -- | 63 |
| SUNLIGHT | FTD/TPI + bevacizumab | 4.47 | -- | 97.56 | 93.09 | -- | -- | -- | 2.44 | -- | -- | -- |
| | FTD/TPI | 6.1 | -- | 97.16 | 91.46 | -- | -- | -- | 2.85 | -- | -- | -- |
| TERRA | FTD/TPI | -- | -- | -- | 23 | -- | -- | 27 | 50 | -- | -- | -- |
| | Placebo | -- | -- | -- | 19 | -- | -- | 27 | 55 | -- | -- | -- |
| Yoshino 2012 | FTD/TPI | -- | -- | -- | 15 | -- | -- | -- | 85 | -- | -- | -- |
| | Placebo | -- | -- | -- | 23 | -- | -- | -- | 77 | -- | -- | -- |

**Key:** BSC, best supportive care; FTD/TPI, trifluridine/tipiracil.



Trials varied in terms of in the proportion of patients who had received prior bevacizumab- or anti-VEGF-containing treatment regimens (Table 21).

**Table 21: Prior bevacizumab or anti-VEGF therapy**

| Trial ID | Arm | Bevacizumab-containing regimens, % | VEGF-containing regimens, % |
|---|---|---|---|
| CONCUR | Regorafenib | -- | -- |
| | Placebo | -- | -- |
| CORRECT | Regorafenib | 100 | -- |
| | Placebo | 100 | -- |
| Pfieffer 2020 | FTD/TPI | 85 | -- |
| | FTD/TPI + bevacizumab | 77 | -- |
| RECOURSE | FTD/TPI | 100 | -- |
| | Placebo | 100 | -- |
| SUNLIGHT | FTD/TPI + bevacizumab | -- | 72.36 |
| | FTD/TPI | -- | 71.54 |
| TERRA | FTD/TPI | 19 | -- |
| | Placebo | 20 | -- |
| Yoshino 2012 | FTD/TPI | 78 | -- |
| | Placebo | 82 | -- |

**Key:** BSC, best supportive care; FTD/TPI, trifluridine/tipiracil; VEGF, vascular endothelial growth factor.

#### *B.2.9.2.6 Outcome definitions and availability*

CONCUR, CORRECT, Pfieffer 2020, RECOURSE, SUNLIGHT, and TERRA, reported investigator-assessed (IA) PFS, and Yoshino 2012 reported both IRC and IA PFS (Table 22).

**Table 22: Outcome definitions**

| Trial ID | OS definition | PFS definition | PFS assessment method |
|---|---|---|---|
| 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 randomization to first radiological or clinical observation of disease progression or any cause death | IA |
| Pfieffer 2020 | Death due to any cause or censored at cut-off date | From the date of randomisation to the first date of radiological or | IA |

| Trial ID | OS definition | PFS definition | PFS assessment method |
|---|---|---|---|
| | | clinical progression, time of death, or censored on cut-off date | |
| RECOURSE | Time from randomisation to death from any cause | Time from randomisation 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 randomization and the date of radiologic tumour progression or death from any cause | IA |
| TERRA | Time from the date of randomisation to the death date | Time from the date of randomisation until the date of radiological disease progression or death due to any cause | IA |
| Yoshino 2012 | Time between randomization and death from any cause or the date of last follow-up | Time between randomization and disease progression or death from any cause | IRC and IA |

**Key:** IA, investigator-assessed; IRC, independent review committee; OS, overall survival; PFS, progression-free survival

#### *B.2.9.2.7 Summary of feasibility*

The target population was patients undergoing third-line treatment for metastatic CRC. 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 trifluridine-tipiracil versus. placebo. Three methods were used to investigate the treatment effect by the number of prior regimens and further information regarding this analysis can be found in Appendix P

1. interaction term analysis in a univariate model
2. interaction term analysis in a multivariate model
3. 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 tumour 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 trifluridine-tipiracil versus. Placebo.

In all analyses, there was no conclusive evidence that line of treatment modifies the relative treatment effects of studies included in the feasibility assessment.

NICE methods guide 3.4.7[58] states that potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline. Therefore, Servier sought clinical opinion on the matter. Clinical insights given to the company from all six NHS consultants unanimously stated that treatment line was not an effect modifier. They also stated that treatment lines are not really the correct way of interpretating outcomes in mCRC as it is considered much more accurate to look at prior treatments. However, the complexities of carrying out a search criteria for a literature review considering this, are wide and varied. One advisor stated you would not consider line of treatment to be a treatment effect modifier in the context of a randomised controlled trial as regardless of 2L or 3L both lines would have an equal advantage.[4]

Therefore, based on the analysis and clinical opinion, it was considered feasible to include studies evaluating different proportions of patients undergoing 3L 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. This was also reinforced in a previous NICE appraisal with Regorafenib (TA866).[45] Similarly, there were differences in patients receiving prior bevacizumab or anti-VEGF treatment. Clinical opinion given to the company were that patients who received prior bevacizumab in previous lines of treatment gained a similar benefit to those that did not[4] and it was also noted in TA866[45] that there was no biological reason for the effect of trifluridine-tipiracil to differ in people who did or did not have biological treatments. However, the conclusion in TA866[45] was although there is uncertainty because of the heterogeneity between trial populations, regorafenib is likely to provide similar benefits in terms of progression-free and overall survival compared to trifluridine-tipiracil. This was further substantiated by clinical opinion to Servier.[4]

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.

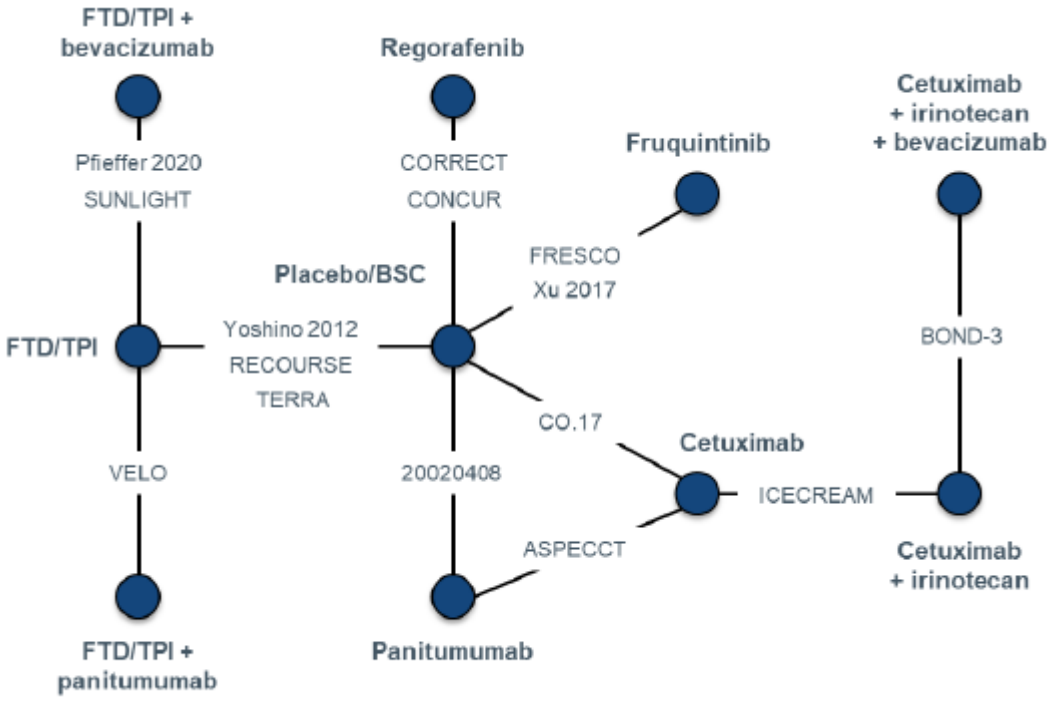
NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18[59] states submissions using anchored population adjustment must produce evidence that population adjustment is likely to produce less biased estimates than would be available through standard indirect comparisons. This requires (i) showing there are grounds for believing one or more of the available covariates is an effect modifier, and (ii) showing that there is sufficient imbalance in those effect modifiers to result in a material bias, in relation to the observed relative treatment effect. However, as this is not available, an NMA was deemed appropriate.

Figure 16 presents the network of studies included in the analysis. As only trifluridine-tipiracil, regorafenib and BSC are relevant comparators in this submission,

only the results of these have been taken forward for the model and presented in the results section.

**Figure 16: Network of studies included in the analyses**



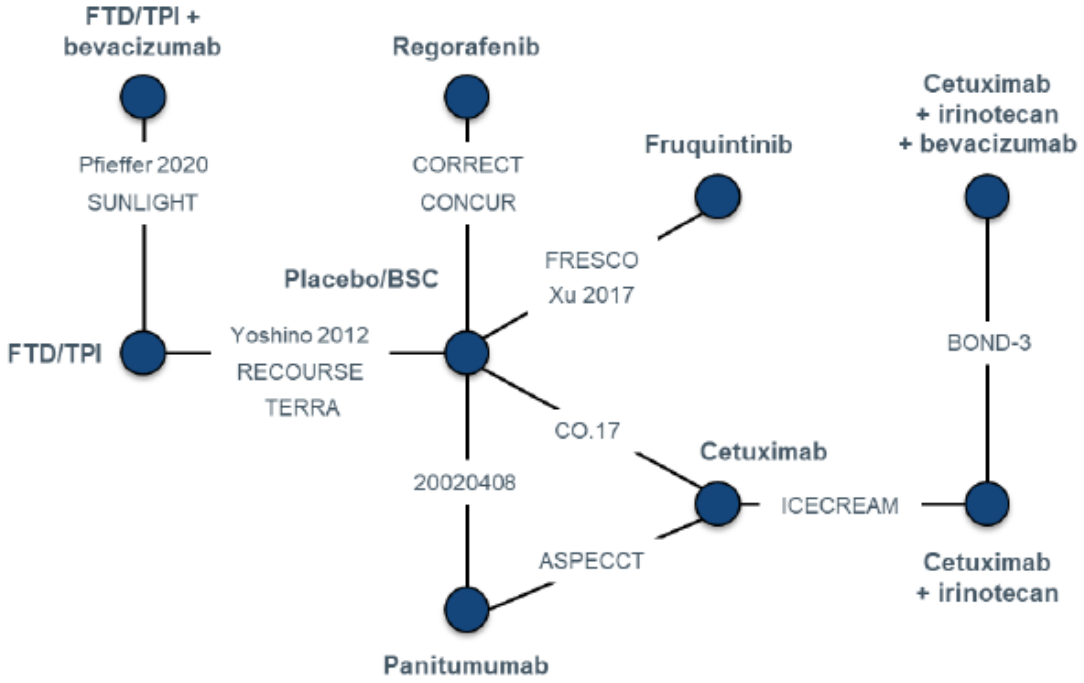

**Note:** Studies identified that were directly related to the decision problem are: CORRECTt[50], CONCUR[49], Yoshino[54], RECOURSE[60], TERRA[53], Pfeiffer[51], and SUNLIGHT.[47]

### B.2.9.3 Results

#### *B.2.9.3.1 Overall survival*

The network for OS included 14 trials evaluating nine different treatment regimens (Figure 17). Of these, only trifluridine-tipiracil with bevacizumab, trifluridine-tipiracil monotherapy, BSC and regorafenib are considered for the cost-effectiveness analysis.

**Figure 17: Network of evidence for OS**




**Note:** Studies identified that were directly related to the decision problem are: CORRECT[50], CONCURr[49], Yoshino[54], RECOURSe[60], TERRA[53], Pfeiffer[51], and SUNLIGHT.[47]

In the random-effects NMA model, trifluridine-tipiracil plus bevacizumab had statistically favourable effects on OS relative to trifluridine-tipiracil, and placebo/BSC. The HR point estimate for OS also favoured trifluridine-tipiracil plus bevacizumab over regorafenib (Table 23). In the fixed-effects NMA model, trifluridine-tipiracil plus bevacizumab had statistically favourable effects on OS relative to trifluridine-tipiracil, regorafenib, and placebo/BSC (Table 24).

The NMA results show external validity as they closely align with those reported in the NMA from a previous NICE appraisal TA866 where regorafenib versus placebo was calculated at 0.68 (0.59, 0.78) and trifluridine/tipiracil versus placebo at 0.68 (0.62, 0.76).[45] Regorafenib versus trifluridine/tipiracil was identical at 0.99 (0.84, 1.17).[45] This is also strongly aligned with clinical insights given by 6 NHS consultants to the company that they would expect the outcomes (i.e., PFS and OS) of trifluridine-tipiracil monotherapy and regorafenib to be similar.[4]

**Table 23: Results of random-effects NMA for OS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | **0.6 (0.42,0.86)** | 0.61 (0.36,1.06) | **0.42 (0.27,0.64)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 level. Deviance information criterion: 24.38; deviance: 13.13; Standard deviation: 0.15.

**Table 24: Results of fixed-effects NMA for OS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | **0.6 (0.49,0.74)** | **0.6 (0.45,0.8)** | **0.42 (0.33,0.54)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

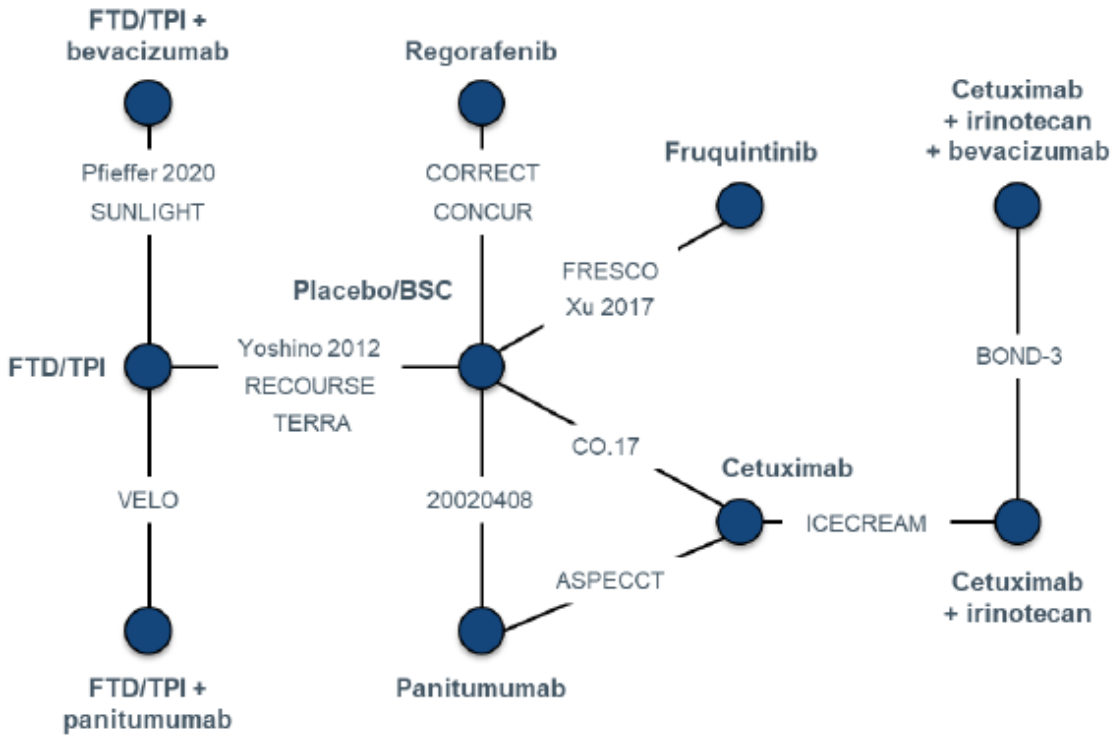
**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 level. Deviance information criterion: 24.53; deviance: 16.54.

#### *B.2.9.3.2 Progression-free survival*

The network for PFS included 15 trials evaluating 10 different treatment regimens (Figure 18). Of these, only trifluridine-tipiracil with bevacizumab, trifluridine-tipiracil monotherapy, BSC and regorafenib are considered for the cost-effectiveness analysis.

**Figure 18: Network of evidence for PFS**




**Note:** Studies identified that were directly related to the decision problem are: Correct[50], Concur[49], Yoshino[54], Recourse[60], Terra[53], Pfeiffer[51], and SUNLIGHT.[47]

In the fixed-effects and random-effects NMA models, trifluridine-tipiracil plus bevacizumab had statistically favourable effects on PFS relative to trifluridine-tipiracil, regorafenib, and placebo/BSC (Table 25 and Table 26).

Once again, with PFS, the NMA results show external validity as they closely align with those reported in the NMA from a previous NICE appraisal TA866 where regorafenib versus placebo was calculated at 0.42 (0.39, 0.45) and trifluridine-tipiracil versus placebo at 0.45 (0.42, 0.48).[45] Regorafenib versus trifluridine-tipiracil was similar at 0.93 (0.85, 1.03).[45] This is also strongly aligned with clinical insights given by 6 NHS consultants to the company that they would expect the outcomes (i.e., PFS and OS) of trifluridine-tipiracil monotherapy and regorafenib to be similar.[4]

**Table 25: Results of random-effects NMA for PFS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | **0.45(0.32,0.63)** | **0.47 (0.29,0.82)** | **0.2 (0.13,0.31)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. Deviance information criterion: 26.52; deviance: 14.19; Standard deviation: 0.15.

**Table 26: Results of fixed-effects NMA for PFS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | **0.44(0.37,0.54)** | **0.45 (0.34,0.58)** | **0.2 (0.16,0.25)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. Deviance information criterion: 26.72; deviance: 17.69.

### B.2.9.4 Conclusion

The random-effects NMA showed that trifluridine-tipiracil plus bevacizumab had statistical superiority over placebo/BSC, and trifluridine-tipiracil, for both OS and PFS as well as over regorafenib for PFS, and fixed-effects NMA showed that trifluridine-tipiracil plus bevacizumab had statistical superiority over placebo/BSC, trifluridine-tipiracil, and regorafenib for both OS and PFS. Also, in both random-effects and fixed-effects NMA, the HR point estimates favoured trifluridine-tipiracil plus bevacizumab over all comparators for both outcomes.

### B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

The SLR involved highly sensitive searches in the peer-reviewed literature, as well as searches of recent conferences and clinical trial registries guided by pre-defined eligibility criteria. Data quality was ensured through involvement of two reviewers in the study selection and data extraction phases of the project. After identifying relevant studies in the SLR, detailed feasibility assessment was carried out to identify trials that could serve as sources of bias in the NMA.

Despite the strengths of this SLR and NMA, some limitations should be acknowledged. First, although the SLR and feasibility assessment were conducted so that studies included in the NMA were similar, between study heterogeneity

modifying the relative treatment effects of included studies may bias the analyses. However, efforts were made to explore potential effect modifiers such as ethnicity and line of treatment to ensure differences in included trials did not bias the results. Second, although it would have been informative to evaluate the comparative efficacy of different treatment regimens delivered specifically in the third-line setting, few studies involved a pure third-line population and analyses did not show any evidence of treatment line being a treatment effect modifier. Two included trials (CORRECT and CONCUR) evaluating the same comparison, regorafenib versus. placebo, reported substantially different results (HRs for OS: 0.55 vs. 0.77, respectively). This implies some differences between the population and study design and potential effect modification, but no conclusive explanations were found and unobserved effect modifiers may be present in the networks. However, the use of random-effects NMA models can account for some effect modification by including a parameter for between study heterogeneity. In addition, these trials were pooled for the TA866 submission and were then considered generalisable for the decision problem.[45]

The NMA was based on reported HRs and, therefore, proportional hazards were assumed. Because HRs between included treatments may change over time, this assumption may over- or under-estimate the advantage of different treatments at particular timepoints, and extrapolations should be considered with caution.

### *B.2.10 Adverse reactions*

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.

As of the clinical cut-off date, treatment duration (mean [SD]; median) was longer for patients receiving trifluridine-tipiracil plus bevacizumab than for patients receiving trifluridine-tipiracil 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 trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil monotherapy group (6.0 [±4.1], 5.0 vs. 3.4 [±2.4], 2.0). In the trifluridine-tipiracil plus bevacizumab group,

15.8% of patients initiated >10 cycles of treatment compared to 2.4% of patients in the trifluridine-tipiracil monotherapy group[2]

At the data cut-off, 36 patients (7.3%) were still receiving treatment: 13.0% in the trifluridine-tipiracil plus bevacizumab group and 1.6% in the trifluridine-tipiracil 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 trifluridine-tipiracil monotherapy group (21.1%) than in the trifluridine-tipiracil plus bevacizumab group (10.6%). The other most frequent reason for treatment withdrawal was adverse events (6.5% in each group).

The overall safety summary is provided in Table 27. 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

**Table 27: Overall safety summary for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, N= 492 [SS])**

| Event (any cause), n (%) | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil monotherapy (n=246) |
|---|---|---|
| Overall AE | 241 (98.0) | 241 (98) |
| Severe (Grade ≥3) AE | 178 (72.4) | 171 (69.5) |
| Serious AE | 61 (24.8) | 77 (31.3) |
| AE leading to trifluridine-tipiracil withdrawal | 31 (12.6) | 31 (12.6) |
| Dose reductions | 40 (16.3) | 31 (12.2) |
| Dose delays | 171 (69.5) | 131 (53.3) |

**Source**: (Servier 2022, Prager 2023b) CSR table (13.3) 1

**Key:** 3L, third-line; AE, adverse event; CSR, clinical study report; mCRC, metastatic colorectal cancer; SS, safety set

TEAEs occurred at a higher frequency in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil monotherapy group: 90% vs. 81% (Table 28). Overall, 89.8% of the patients in the combination group and 81.3% in the trifluridine-tipiracil monotherapy group had AEs that were attributed by the investigator to trifluridine-tipiracil, and 48.4% of the patients in the combination group had bevacizumab-related events[46]

Consistent with previous studies, the most common (>20%) TEAEs (related to trifluridine-tipiracil and/or bevacizumab) observed in either treatment group were predominantly haematologic and gastrointestinal in nature: neutropenia, anaemia, and nausea. Neutropenia and nausea occurred at higher frequency with trifluridine-tipiracil plus bevacizumab than with trifluridine-tipiracil monotherapy (neutropenia: 62.2% vs. 51.2%; nausea: 37.0% vs. 27.2%) and anaemia occurred with similar frequency in the two treatment groups (28.9% vs. 31.7%). Other TEAEs occurring at higher frequency with trifluridine-tipiracil plus bevacizumab were thrombocytopenia (17.1% vs. 11.4%), vomiting (18.7% vs. 14.6%), neutrophil count decreased (13.8% vs. 6.9%), stomatitis (11.0% vs. 3.7%), platelet count decreased (8.9% vs. 2.0%) and hypertension (10.2% vs. 2.0)[2] . The TEAE observed in the study are in line with the known and expected adverse events associated with the individual products [5]

**Table 28: Overall treatment-related safety summary for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, N= 492 [SS])**

| Event (any cause), n (%) | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil monotherapy (n=246) |
|---|---|---|
| Trifluridine-tipiracil-related AE | 221 (89.8) | 200 (81.3) |
| Bevacizumab-related AE | 119 (48.4) | NA |

**Source**: (Prager 2023b)

**Key:** 3L, third-line; AE, adverse event; mCRC, metastatic colorectal cancer; NA, not applicable; SS, safety set

The ten most frequent TEAE are described by Grade in Appendix F. Among the ten most frequent TEAEs in the trifluridine-tipiracil plus bevacizumab group, the majority were of Grade 1 or Grade 2, except neutropenia (3.3% Grade 1, 15.4% Grade 2, 28.9% Grade 3, 12.6% Grade 4) and neutrophil count decreased (none Grade 1, 4.9% Grade 2, 5.7% Grade 3, 3.3% Grade 4). Among the ten most frequent TEAEs in the trifluridine-tipiracil monotherapy group, the majority were rated Grade 1 or Grade 2, except neutropenia (1.2% Grade 1, 17.9% Grade 2, 20.3% Grade 3, 8.9% Grade 4) and anaemia (6.9% Grade 1, 10.2% Grade 2, 8.1% Grade 3, none Grade 4)[2]

Overall, there were no new safety signals or unexpected toxicities with the trifluridine-tipiracil plus bevacizumab combination.

Severe TEAEs were reported at higher frequency in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil monotherapy group: 58.9% vs. 45.5% (Table 29)[2].The most frequent (>5%) severe TEAE experienced at a higher rate with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy were neutropenia (41.5% vs. 29.3%) and neutrophil count decreased (8.9% vs. 5.3%). Although the trifluridine-tipiracil plus bevacizumab group had higher incidence of neutropenia, the incidence of febrile neutropenia was lower in this group compared with trifluridine-tipiracil monotherapy (0.4% vs. 2.4%). Conversely, anaemia was reported less frequently in the trifluridine-tipiracil plus bevacizumab group than in the trifluridine-tipiracil monotherapy group (4.9% vs. 8.1%). Hypertension was reported only in the trifluridine-tipiracil plus bevacizumab group (4% vs. 0%) with all instances of hypertension in the trifluridine-tipiracil plus bevacizumab group related to bevacizumab, except for one case which was related to both trifluridine-tipiracil and bevacizumab.[2] This is consistent with the known safety profile of bevacizumab.[61]

In contrast, patients experienced a lower rate of serious TEAEs with trifluridine-tipiracil plus bevacizumab than with trifluridine-tipiracil monotherapy (Table 29). Serious TEAEs were reported for 13 patients (5.3%) in the trifluridine-tipiracil + bevacizumab group and 20 (8.1%) patients in the trifluridine-tipiracil group. Serious TEAEs that occurred in more than 2 (0.8%) patients were febrile neutropenia and anaemia (0.4% vs. 2.4% for each) [2]

Table 29: Severe and serious TEAE in patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, N=492 [SS])

| TEAEs*, n (%) | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| Severe TEAE (Grade ≥3)** | 145 (58.9%) | 112 (45.5%) |
| Neutropenia | 41.5% | 29.3% |
| Anaemia | 4.9% | 8.1% |
| Neutrophil count decease | 8.9% | 5.3% |
| Hypertension | 4.1% | 0% |
| Serious TEAE*** | 13 (5.3%) | 20 (8.1%) |
| Febrile neutropenia | 1 (0.4%) | 6 (2.4%)[#] |

**Source**:(Servier 2022) [2]

**Notes**: TEAEs were graded by the investigators (Grade 1 to 5) according to the CTCAE Version 5.0. *TEAE are those events that occurred on treatment period related to the combination, i.e. related to trifluridine-tipiracil and/or bevacizumab, unless specified otherwise. **TEAE ≥Grade 3 were considered as severe. ***Serious TEAE were described for each treatment arm according to the worst Grade, the severity, the relationship to IMPs, the relationship to disease progression, the actions taken regarding IMPs, the requirement of added therapy, and the outcome. #One event of the six registered had a severity level of Grade 2

**Key**: 3L, third-line; IMP, investigational medicinal product; mCRC, metastatic colorectal cancer; SS, safety set; TEAE, treatment-related emergent adverse events

Incidence of TEAEs leading to withdrawal and/or death was minimal for both trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil monotherapy arms (Table 30). TEAEs leading to withdrawal were reported at similar frequency with trifluridine-tipiracil plus bevacizumab and with trifluridine-tipiracil monotherapy. TEAEs leading to withdrawal in more than 1 (0.4%) patient were anaemia (0.4% vs. 0.8%) and fatigue (none vs. 0.8%). None of the fatal AE were considered treatment-related in either group (Table 30). Dose reductions occurred in 16.3% of the patients in the combination group and in 12.2% in the trifluridine-tipiracil monotherapy group; dose delays occurred in 69.5% and 53.3%, respectively.[46]

**Table 30: TEAE leading to trifluridine-tipiracil withdrawal or death in patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, N=492 [SS])**

| n, (%) | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| TEAEs leading to withdrawal | 6 (2.4%) | 5 (2.0%) |
| TEAEs leading to death | 0 (0%) | 0 (0%) |

**Source**:(Servier 2022) CSR page 100 and table (13.3)[2]

**Notes**: TEAEs were graded by the investigators (Grade 1 to 5) according to the CTCAE Version 5.0

**Key**: 3L, third-line; CSR, clinical study report; mCRC, metastatic colorectal cancer; SS, safety set; TEAEs, treatment-related emergent adverse events

### *B.2.11 Ongoing studies*

No additional ongoing studies planned.

### *B.2.12 Interpretation of clinical effectiveness and safety evidence*

Trifluridine-tipiracil plus bevacizumab establishes a new treatment standard for 3L mCRC patients who received two prior regimens, showing significant and clinically meaningful improvements in OS and PFS, while maintaining HRQoL and preserving a tolerable safety.

SUNLIGHT is the first Phase 3 clinical trial comparing to an active comparator that demonstrates extended survival in patients with 3L mCRC. Trifluridine-tipiracil has transformed patient care in 3L mCRC, leading to a marked improvement in median OS from 5.2 months (RECOURSE trial, placebo arm) to 7.2 months (RECOURSE trial, trifluridine-tipiracil arm). Trifluridine-tipiracil plus bevacizumab provides a further increase in OS with an additional 3.3 months versus trifluridine-tipiracil monotherapy (median OS: 10.8 months vs. 7.5 months with trifluridine-tipiracil monotherapy) and has demonstrated a consistent survival benefit across all pre-specified subgroups

Patients who received trifluridine-tipiracil plus bevacizumab experienced a significant improvement in PFS compared to trifluridine-tipiracil monotherapy, with PFS increased by 3.2 months with the combination (5.6 months vs. 2.4 months, respectively).

Trifluridine-tipiracil plus bevacizumab significantly delayed the time to a decline in HRQoL, with HRQoL maintained for an additional 3.8 months with trifluridine-tipiracil plus bevacizumab compared with trifluridine-tipiracil monotherapy (as measured by a time to deterioration in EORTC QLQ C30 GHS). Trifluridine-tipiracil plus bevacizumab also delayed the time to deterioration in ECOG PS ≥2 by 3.0 months, indicating a decline in their ability to carry out daily activities and self-care (9.3 months vs. 6.3 months with trifluridine-tipiracil monotherapy)

Trifluridine-tipiracil plus bevacizumab has demonstrated a manageable safety profile, consistent with the individual safety profiles of each product

Overall, trifluridine-tipiracil plus bevacizumab represents a new standard of care for patients with refractory mCRC who have received two prior chemotherapy regimens and have demonstrated progressive disease or intolerance to their last regimen, building on the established benefits of trifluridine-tipiracil monotherapy.

## B.3 Cost-effectiveness

Trifluridine-tipiracil is a clinically effective option for the treatment of mCRC and after recommendation by NICE in 2016 now represents standard of care for patients with previously treated mCRC. The addition of bevacizumab to trifluridine-tipiracil has been evaluated in SUNLIGHT (a multicentre, randomised, double-blind Phase III study comparing which compares the combination treatment regimen to trifluridine-tipiracil monotherapy).

To assess the cost-effectiveness of trifluridine-tipiracil plus bevacizumab a *de novo* cost-effectiveness model was constructed to compare trifluridine-tipiracil plus bevacizumab to trifluridine-tipiracil monotherapy, regorafenib and BSC.

The SUNLIGHT trial was the primary analysis informing the model efficacy and is well-aligned to the decision problem for the current appraisal and the trial is considered reflective and generalisable to UK clinical practice. The most clinically plausible extrapolations for PFS, OS and time on treatment (ToT) data were selected for the base case analysis (using guidance provided by NICE in relevant technical supporting documentation). To assess additional relevant comparisons (to regorafenib and BSC), which were not evaluated in SUNLIGHT, outcomes from a network-meta-analysis were applied. Parameter uncertainty was tested rigorously through one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA), with structural uncertainty explored in scenario analysis.

The base case modelling approach, including the selected model structure, costing inputs and utility sources are consistent with the methods set out in the NICE reference case, and are broadly aligned with those used in previous appraisals in the mCRC setting (namely TA405 and TA866).

Due to the severity of mCRC, trifluridine-tipiracil plus bevacizumab appears to meet the criteria for the 1.2x severity weighting and the highest severity weighting (1.7x) dependent on the comparator selected to inform the QALY shortfall calculation. As such, analyses have been presented which explore both severity weightings.

In the base case analysis (with a 1.7x weighting applied) the ICER for trifluridine-tipiracil plus bevacizumab was [redacted] versus trifluridine-tipiracil, [redacted] versus BSC and [redacted] versus regorafenib. With a 1.2x weighting applied, the ICER for trifluridine-tipiracil plus bevacizumab was [redacted] versus trifluridine-tipiracil, [redacted] versus BSC and [redacted] versus regorafenib.

Servier is aware that the list price of bevacizumab is likely to vary due to the availability of biosimilars on the market and loss of exclusivity, and this will impact the interpretation of cost-effectiveness throughout the results presented.

### *B.3.1 Published cost-effectiveness studies*

A systematic literature review of the literature was conducted to identify published economic evaluations and cost-effectiveness studies relevant to the decision problem addressed in this appraisal. Electronic data bases were searched on 10th February 2023. Data base searched included Excerpta Medica database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), and EconLit. Additionally, the cost-effectiveness analysis Registry (https://cear.tuftsmedicalcenter.org/) was searched

using key words for the population of interest. As clinical trials of third-line (3L) treatments for advanced and mCRC patients did not appear until after 2010, all search results were limited to publications from 2010 to the present. Results of the economic systematic literature review are reported in Appendix G.

The review identified 7,088 records. After the removal of duplicate records and irrelevant publication types, 2,103 titles/abstracts were screened, resulting in the identification of 96 reports for full-text review. Of these, 63 reports were excluded. After adding 10 reports obtained from searching conference and HTA websites, a total of 43 reports were included in in the systematic literature review. Thirty-five reports were formal cost-effectiveness studies, and eight were descriptive HCRU/cost studies. The thirty-five cost-effectiveness publications were identified from the review and are summarised in Appendix G.

## *B.3.2 Economic analysis*

A *de novo* economic model was constructed to compare trifluridine-tipiracil with bevacizumab. From the SLR of cost-effectiveness studies, one study was identified which considered trifluridine-tipiracil with bevacizumab as the intervention (see Section B.3.1 and Appendix G)This study contained the relevant intervention and treatment setting, however the analysis (and the economic model) was developed in R, using published Phase 2 studies with costs presented in US dollars. As such, with a different perspective (US), different information to inform the efficacy estimates, and insufficient detail to reliably replicate / interpret the economic analyses, the study was deemed unsuitable to support with the current economic evaluation. Despite this, previous economic models submitted to NICE within the mCRC setting were used alongside publications identified within the economic SLR to inform the model structure, assumptions and data sources.

### B.3.2.1 Patient population

The population considered in the cost-effectiveness analysis is adults with mCRC after two systemic treatments. The population is in line with the anticipated marketing authorisation and the final scope issued by NICE. Furthermore, the population is in line with the population in the pivotal trial SUNLIGHT. Patients in the trial had histologically confirmed, unresectable adenocarcinoma of the colon or rectum and

had received no more than two previous chemotherapy regimens for the treatment of advanced colorectal cancer.[46]

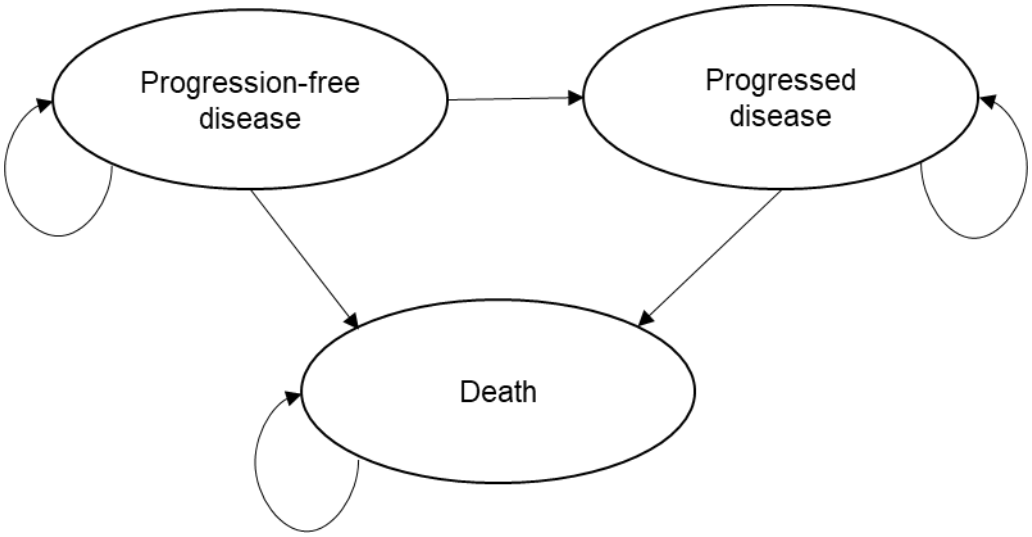
#### B.3.2.2 Model structure

The *de novo* cost-effectiveness model was developed in Microsoft Excel using an area-under-the-curve, partitioned survival analysis (PartSA) structure, where survival curves are used to determine health state occupancy. The model consists of three health states: progression-free, progressed disease and death.

This structure was chosen as progression-based models are commonly used within cost-effectiveness models as they provide an intuitive application of the outcomes seen in cancer-based clinical trials and accurately reflect the progressive nature of mCRC. This allows lifetime costs and health outcomes to be accurately estimated. Furthermore, the model health states are consistent with previous NICE appraisals in mCRC.[44,45]

The model schematic is presented in Figure 19. Patients enter the model in the 'progression-free' health state and in each cycle can transition to 'progressed' or 'death' or remain 'progression-free'. Once a patient progresses, they either remain in the 'progressed' health state or transition to 'death' per model cycle. Death is an absorbing state.

**Figure 19: Model schematic**



Health state occupancy is determined by independently modelled but non-mutually exclusive progression-free survival (PFS) and overall survival (OS) curves. The proportion of patients in each health state is then calculated as follows:

- Progression-free = PFS
- Progressed = OS – PFS
- Death = 1 – OS

ToT curves are used to calculate the proportion of patients on treatment for the calculation of drug costs. Details of how the OS, PFS and ToT curves are derived are provided in Section B.3.3.

#### *B.3.2.2.1 Model settings*

As per the NICE reference case, all health effects were measured in quality-adjusted life years (QALYs) with a 3.5% discount applied to costs and QALYs. [58] The analysis is conducted from the perspective of the NHS and Personal Social services (PSS).[58]

The NICE reference case stipulates that the time horizon of economic models should be long enough to reflect all important differences in costs or outcomes between technologies.[58] As such, the cost-effectiveness analysis adopts a lifetime horizon or 15-years, which was considered long enough to adequately capture the lifetime of patients with mCRC after two systemic treatments. The model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for patients with mCRC, being treated with trifluridine/tipiracil or a comparator. Due to the short cycle length, a half-cycle correction is not applied.

A summary of the key features of the economic analysis is presented in Table 31 in comparison to previous NICE appraisals in previously treated mCRC. It should be noted that, while TA668 considered patients with previously treated mCRC, the population in that evaluation was specifically those with BRAF V600E mutation-positive mCRC. Encorafenib plus cetuximab is not considered a relevant comparator within the context of this appraisal (as outlined in Section B.3.2.3.2) but has been included in Table 31 for completeness in comparing across previous evaluations in the mCRC setting.

**Table 31: Features of the economic analysis**

| | Previous evaluations | | | Current evaluation | |
|---|---|---|---|---|---|
| **Factor** | **TA405 – trifluridine/tipiracil** | **TA866 - Regorafenib** | **TA668 – Encorafenib plus cetuximab** | **Chosen values** | **Justification** |
| Perspective | NHS and PSS | NHS and PSS | NHS and PSS | NHS and PSS | Consistent with NICE reference case |
| Model type | PartSA | PartSA | PartSA | PartSA | Reflects the natural history of mCRC (progressive disease).<br>Consistent with previous models in mCRC and other oncology indications |
| Time horizon | 10 years | 10 years | 10 years | 15 years | 15 years considered sufficiently long to capture the full extent of both costs and effects as < 1% alive at the end of the time horizon. Different time horizons explored in sensitivity analysis |
| Cycle length | Daily | 1 week | 1 month | 1 week | A 1-week cycle length was considered short enough to adequately capture meaningful changes in health status |
| Half-cycle correction | No | Yes | Yes | No | Half-cycle correction was not considered |

| | Previous evaluations | | | Current evaluation | |
|---|---|---|---|---|---|
| **Factor** | **TA405 – trifluridine/tipiracil** | **TA866 - Regorafenib** | **TA668 – Encorafenib plus cetuximab** | **Chosen values** | **Justification** |
| | | | | | necessary due to the short cycle length |
| Discount rate | 3.5% for costs and QALYs | 3.5% for costs and QALYs | 3.5% for costs and QALYs | 3.5% for costs and QALYs | Consistent with NICE reference case |
| Source of utilities | Average of CORRECT study and TA176 | Average EQ-5D scores from CORRECT and CONCUR | BEACON-CRC | EQ-5D-5L from SUNLIGHT mapped to EQ-5D-3L (Hernández Alava et al. mapping function) | Consistent with NICE reference case |
| Source of costs | NHS reference costs, PSSRU.<br>Where unavailable from these sources, published literature or previous NICE appraisals are cited and justified | BNF, NHS reference costs, PSSRU | BNF, NHS reference costs, PSSRU, and eMIT | A range of standard reference sources including BNF, NHS NCC, PSSRU and eMIT | Consistent with NICE reference case |

**Key:** BNF, British National Formulary; eMIT, electronic market information tool; NCC, National Cost Collection; NHS, National Health Service; PartSA, partitioned survival analysis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TA, technology appraisal

### B.3.2.3 Intervention technology and comparators

#### *B.3.2.3.1 Intervention*

The intervention considered within the scope of this evaluation is trifluridine-tipiracil in combination with bevacizumab. Trifluridine-tipiracil with bevacizumab is incorporated into the analysis according to its anticipated marketing authorisation and in line with the decision problem described in Section B.1.1.

As described in Section B.1.2, trifluridine-tipiracil is an oral cytotoxic chemotherapy, administered at a dose of 35 mg/m$^2$ twice daily on days 1 to 5 and 8 to 12 of each 28-day treatment cycle. This dose is aligned with how trifluridine-tipiracil was administered in the SUNLIGHT trial[46], and is representative of the expected marketing authorisation for the combination with bevacizumab. This dose is also aligned with the current marketing authorisation for the treatment of mCRC for trifluridine-tipiracil monotherapy.[62]

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A). Bevacizumab is administered intravenously at a dose of 5 mg/kg every two weeks. This is consistent with the dose received in the SUNLIGHT study[46] and current marketing authorisation for mCRC.[61]

Treatment is continued until disease progression or unacceptable toxicity. If a patient discontinues trifluridine-tipiracil then bevacizumab would also be discontinued. However, patients can continue with trifluridine-tipiracil if needing to discontinue bevacizumab.

#### *B.3.2.3.2 Comparators*

The final scope issued by NICE highlights nine potential comparators to trifluridine-tipiracil with bevacizumab:

- Single agent irinotecan
- FOLFIRI
- FOLFOX
- Raltitrexed
- Trifluridine-tipiracil monotherapy

- Regorafenib
- Nivolumab plus ipilimumab
- Encorafenib plus cetuximab
- Best supportive care

As described in Section B.1.1 treatment options at third-line mCRC currently consist of trifluridine-tipiracil monotherapy, regorafenib or best supportive care, all of which are included as comparators within the economic evaluation. This approach is aligned with the treatment pathway presented in TA866 (regorafenib for previously treated metastatic colorectal cancer) and is consistent with feedback received from clinical experts who stated that currently they would consider either trifluridine-tipiracil, regorafenib or best supportive care in the third-line setting.[4]

## *B.3.3 Clinical parameters and variables*

Throughout this section, model efficacy estimates are presented based on the ITT population of the SUNLIGHT study considered within the final scope provided by NICE. A subgroup analysis which considers a patient population within SUNLIGHT who have received no prior bevacizumab is presented in Section B.3.12. All corresponding efficacy assumptions for the subgroup are presented in Appendix M.

### B.3.3.1 Baseline patient characteristics

Baseline patient characteristics were based on the population in the SUNLIGHT trial and are presented in Table 32. Mean age and the proportion of female patients were used in the economic model to calculate age- and sex-matched general population mortality rates and estimate corresponding health-related quality of life. Weight and body surface area (BSA) data from the trial was used to calculate drug acquisition costs for treatments with a weight-based dosing regimen (discussed further in Section B.3.5.1.1).

**Table 32: Baseline patient characteristics**

| Characteristic | Value | Source |
|---|---|---|
| Age (years) | 61.68 | SUNLIGHT[2] |
| Proportion female | 47.97% | |
| Weight | 74 kg | |
| BSA | 1.83 $m^2$ | |

**Key:** BSA, body surface area; kg, kilogram

### B.3.3.2 Clinical effectiveness

Efficacy data from the open-label, multi-national, randomised Phase 3 SUNLIGHT trial were used to inform OS, PFS and ToT within the economic model for trifluridine-tipiracil with bevacizumab (n=246) and trifluridine-tipiracil (n=246) using the ITT population (n=492), from the latest SUNLIGHT data cut (19 July 2022). The trial is discussed in detail in Section B.2.6. Efficacy for the other comparators (regorafenib and BSC) were based on results from an NMA, which is described in Section B.2.9.

Although data were relatively mature, survival modelling was required to inform the economic model to extrapolate over the trial period to estimate costs and QALYs over a lifetime horizon. Due to the availability of patient-level data and the maturity of the evidence available, independent curves were fitted to the data for all time-to-event outcomes (OS, PFS, ToT). Log cumulative hazard plots (LCHPs) were produced to evaluate whether the relative hazard of two different interventions changes over time or any hazard ratio (HR) applied can reasonably be assumed to be time-invariant. Prior to fitting the parametric survival models (PSMs), a LCHP and quantile-quantile (Q-Q) plot was produced for time-to-event outcomes to assess if the assumption of proportion hazards (PH) and acceleration failure time (AFT) is likely to hold across the treatments. Should the PH assumption be judged to hold, the LCHP would indicate that the two curves are parallel. Should the AFT assumption be likely to hold, the Q-Q plot would present points in an approximately positive diagonal straight line running through the origin. These are provided in Appendix N.

PSMs were fitted to OS, PFS and ToT data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to inform the model. The selection of the most appropriate distribution has been made in accordance with the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[63] The visual inspection of extrapolated survival, alongside Akaike and Bayesian information criteria (AIC, BIC) were used to determine the most appropriate model to characterise the observed Kaplan-Meier (KM) data. Clinical validation was sought to help interpret OS and PFS estimates to determine clinical

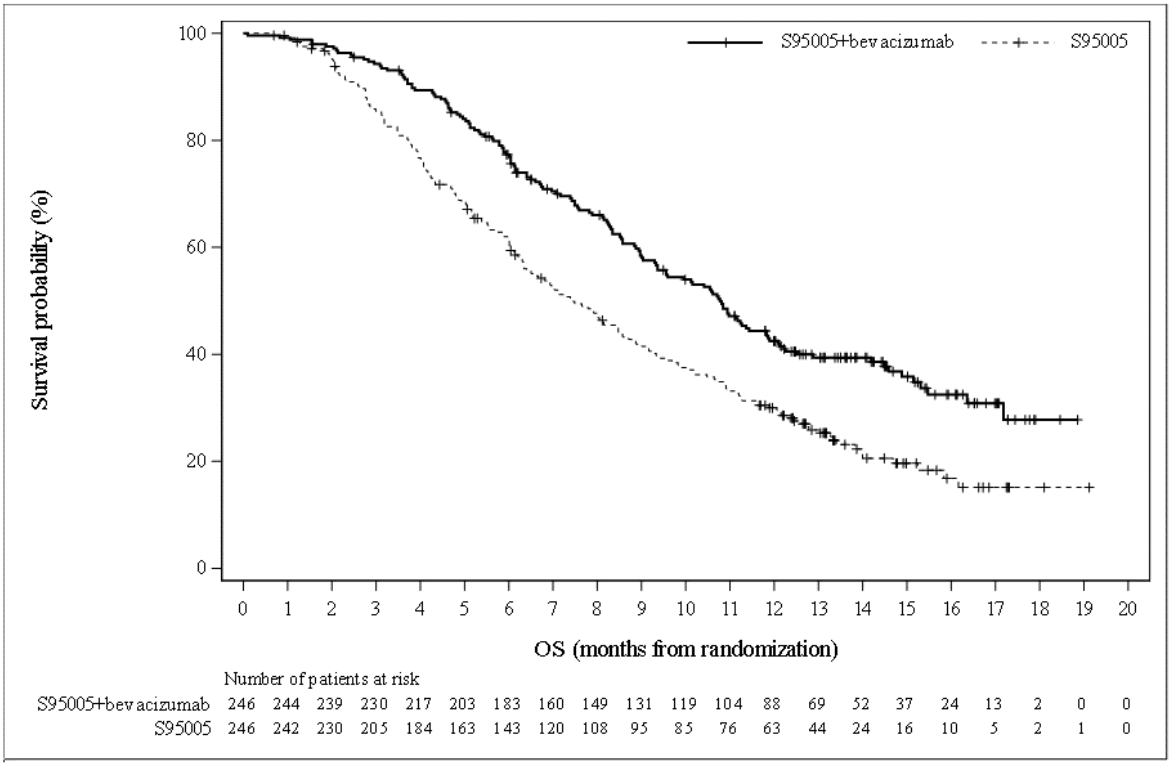

 

plausibility of long-term outcomes and select an appropriate parametric curve to inform the base case distribution. Description of the approach and rationale to inform the base case for OS, PFS and ToT are discussed in turn throughout this section.

#### *B.3.3.2.1 Overall survival*

A summary of the OS data from the SUNLIGHT study is provided in Figure 20. trifluridine-tipiracil plus bevacizumab was associated with a statistically significant and clinically meaningful OS benefit compared to trifluridine-tipiracil monotherapy with an estimated HR of 0.61 (95% confidence interval [CI]: 0.49, 0.77; p<0.001). The median OS was 10.8 months (95% CI: 9.36, 11.83) for the trifluridine-tipiracil plus bevacizumab arm versus 7.5 months (95% CI: 6.34, 8.57) for the trifluridine-tipiracil monotherapy group. Although the KM curves are fairly mature, extrapolation of outcomes was required to inform cost-effectiveness estimates and are provided in Figure 21 and Figure 22 for trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil respectively.

**Figure 20: SUNLIGHT – Kaplan-Meier – OS**




**Key:** OS, overall survival; S95005, trifluridine-tipiracil

**Source:** SUNLIGHT Clinical Study Report[2]

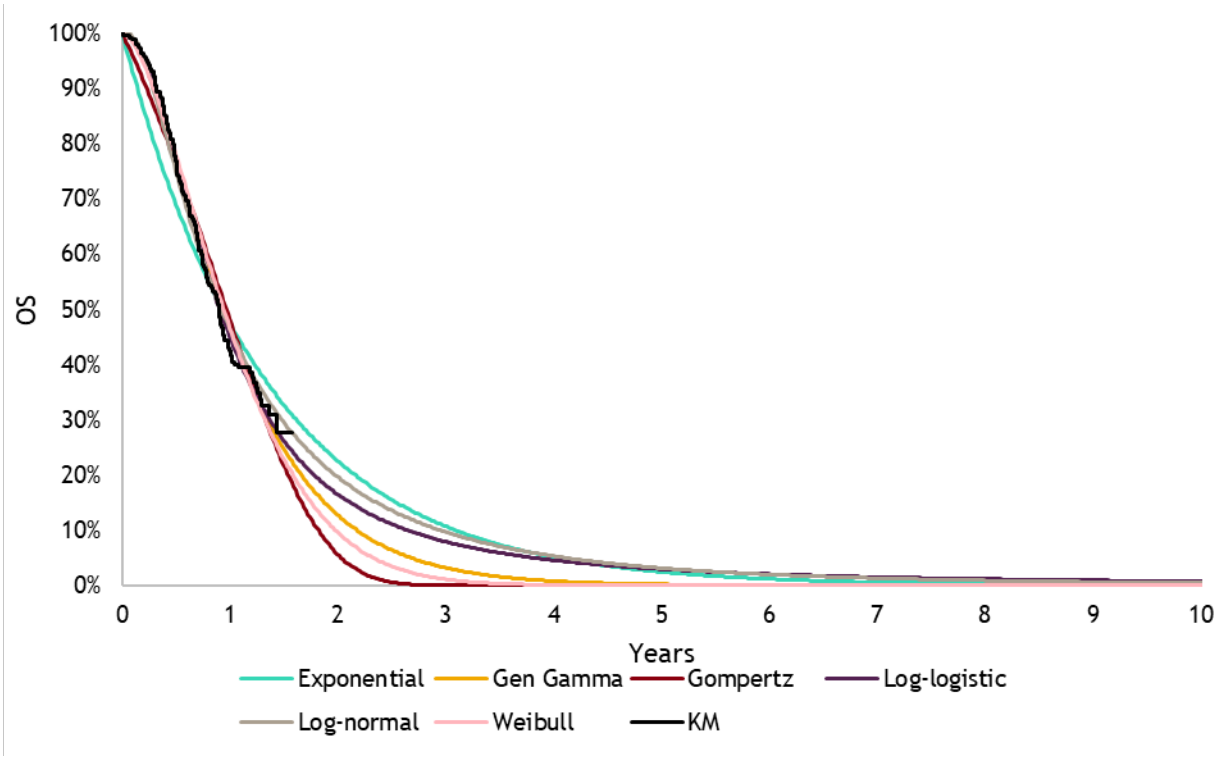
AIC and BIC scores can be used to determine the relative fit of alternative PSMs to the observed data. AIC and BIC for OS PSMs is provided in Table 33. Based on the AIC and BIC scores, the log-logistic model provided the best fit for trifluridine-tipiracil plus bevacizumab and log-normal for the trifluridine-tipiracil arm. Although several of the PSMs have relatively close AIB/BIC statistics to the best fitting curves, some curves indicate a poorer fit with much higher AIC/BIC statistics (e.g., the exponential and Gompertz curves), which could infer a poorer fit for the treatment arms.[64]

**Table 33: Statistical goodness-of-fit scores - OS**

| Parameterisation | Trifluridine-tipiracil plus bevacizumab | | Trifluridine-tipiracil | |
|---|---|---|---|---|
| | AIC | BIC | AIC | BIC |
| Exponential | 1120.5 | 1124.0 | 1230.5 | 1234.0 |
| Generalised gamma | 1084.3 | 1094.8 | 1183.1 | 1193.6 |
| Gompertz | 1099.9 | 1106.9 | 1215.6 | 1222.6 |
| Log-logistic | **1079.4** | **1086.4** | 1184.8 | 1191.8 |
| Log-normal | 1092.7 | 1099.7 | **1181.1** | **1188.1** |
| Weibull | 1084.9 | 1091.9 | 1196.1 | 1203.1 |

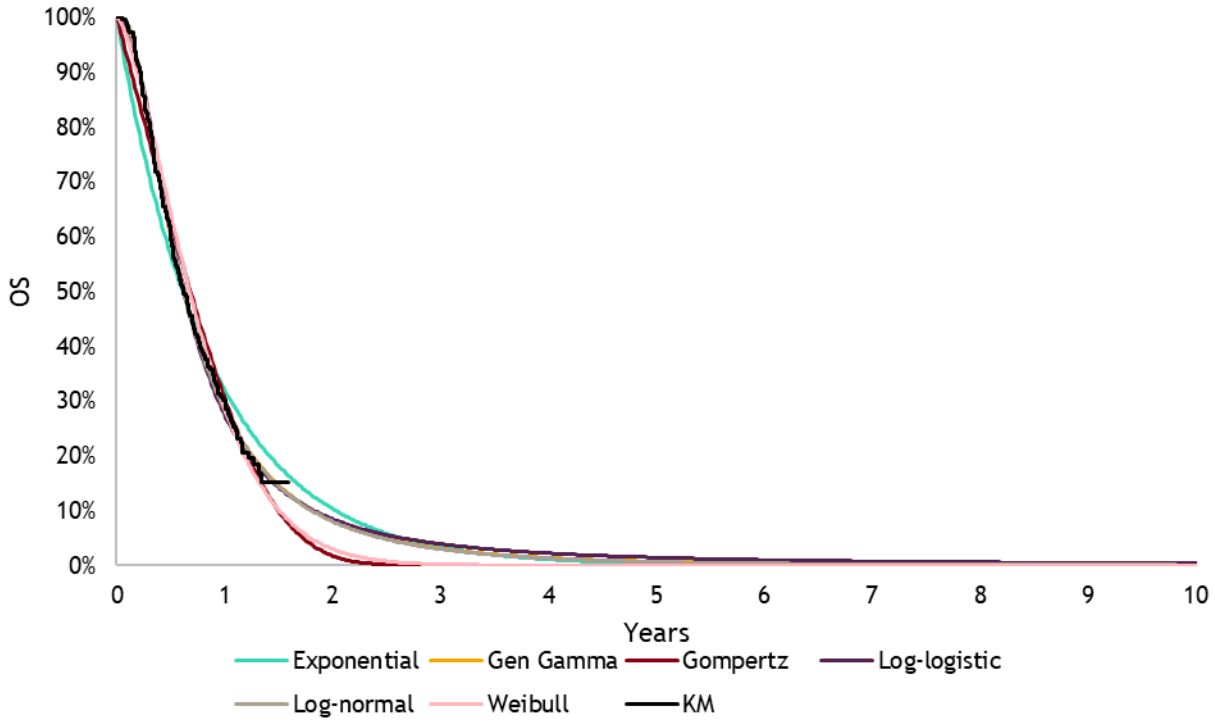
**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

**Figure 21: Parametric curve fits – Trifluridine-tipiracil plus bevacizumab - OS**




**Key:** KM, Kaplan-Meier; OS, overall survival

**Figure 22: Parametric curve fits – Trifluridine-tipiracil - OS**




**Key:** KM, Kaplan-Meier; OS, overall survival

All models appear to fit the observed data reasonably well (with the exception of the exponential distribution). The log-logistic and log-normal are statistically the best fitting extrapolations and project very similar outcomes in the long-term for both treatment arms. Log-logistic and log-normal curves provide a very similar visual fit for trifluridine-tipiracil, though the log-normal provides a poorer visual fit for trifluridine-tipiracil plus bevacizumab (with the curve resting slightly above the observed period in the latter part of the KM).

Six clinicians consulted as part of the submission stated that for trifluridine-tipiracil they would expect between 2-10% alive at 2 years with very few or no patients alive by 5 years.[4] This rules out exponential as a plausible option. One clinician also comments that log-logistic looks the most plausible based on the proportion alive at 4 years (2.2%). For trifluridine-tipiracil plus bevacizumab, the majority of clinicians chose log-logistic as the most plausible curve due to the expectation of 15-20% alive at 2 years and 2.9% alive at 5 years being a reasonable estimate.

Overall, the log-logistic curve was considered appropriate to inform the base case assumptions. For consistency, the same distribution was chosen for both treatment arms. Exploration of the alternative curve fits is considered in scenario analysis.

For regorafenib and BSC, the HRs derived from the NMA (see Section B.2.9) are applied to the trifluridine-tipiracil plus bevacizumab OS curve. The HRs used in the base case are presented in Table 34.

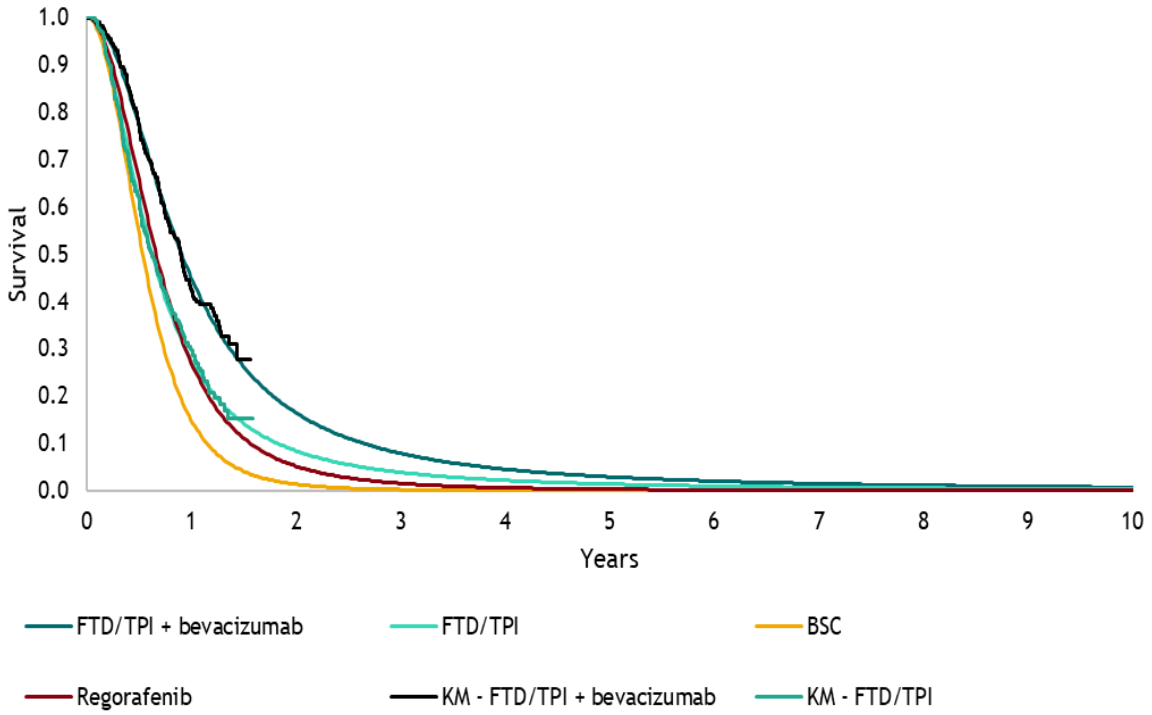
**Table 34: NMA results used in the base case – random-effects – OS**

| Comparator | HR | 95% CrI |
|---|---|---|
| BSC | 0.42 | 0.27 – 0.64 |
| Regorafenib | 0.61 | 0.36 – 1.06 |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis

A summary of the base case OS efficacy for all treatments is presented in Figure 23. Based on the modelled OS, the outcomes for regorafenib are similar to the trifluridine-tipiracil arm. This is aligned with clinical feedback and expectations based on previous technology appraisals[45] (where in TA866, the committee concluded that regorafenib is likely to have similar PFS and OS compared with trifluridine-tipiracil).

**Figure 23: OS base case summary**

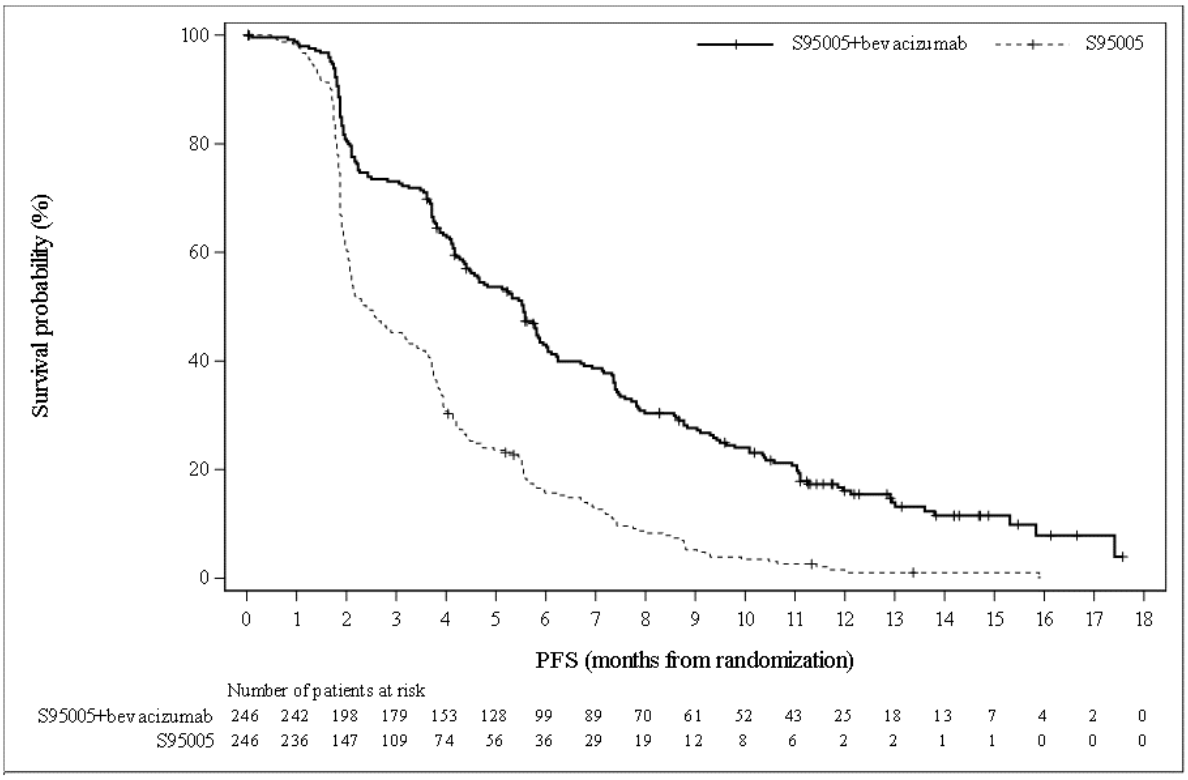



**Key:** BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; KM, Kaplan-Meier; OS, overall survival

#### *B.3.3.2.2 Progression-free survival*

A summary of the PFS data from the SUNLIGHT study is provided in Figure 24. trifluridine-tipiracil plus bevacizumab was associated with a statistically significant improvement in PFS compared to trifluridine-tipiracil monotherapy with an estimated HR of 0.44 (95% CI: 0.36, 0.54; p<0.001). The median PFS was 5.6 months (95% CI: 4.50, 5.88) for the trifluridine-tipiracil plus bevacizumab arm versus 2.4 months (95% CI: 2.07, 3.22) for the trifluridine-tipiracil monotherapy group. The KM curves are quite mature (89.8% of patients had a PFS event) however extrapolation of outcomes was still required to extend the outcomes into the future to inform cost-effectiveness estimates.

**Figure 24: SUNLIGHT – Kaplan-Meier – PFS**




**Key:** PFS, progression-free survival; S95005, trifluridine/tipiracil

**Source:** SUNLIGHT Clinical Study Report[2]

The statistical goodness-of-fit of all fitted PSMs is provided in Table 35 with the PSMs for trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil plus bevacizumab shown in Figure 25 and Figure 26 respectively. Based on the AIC and

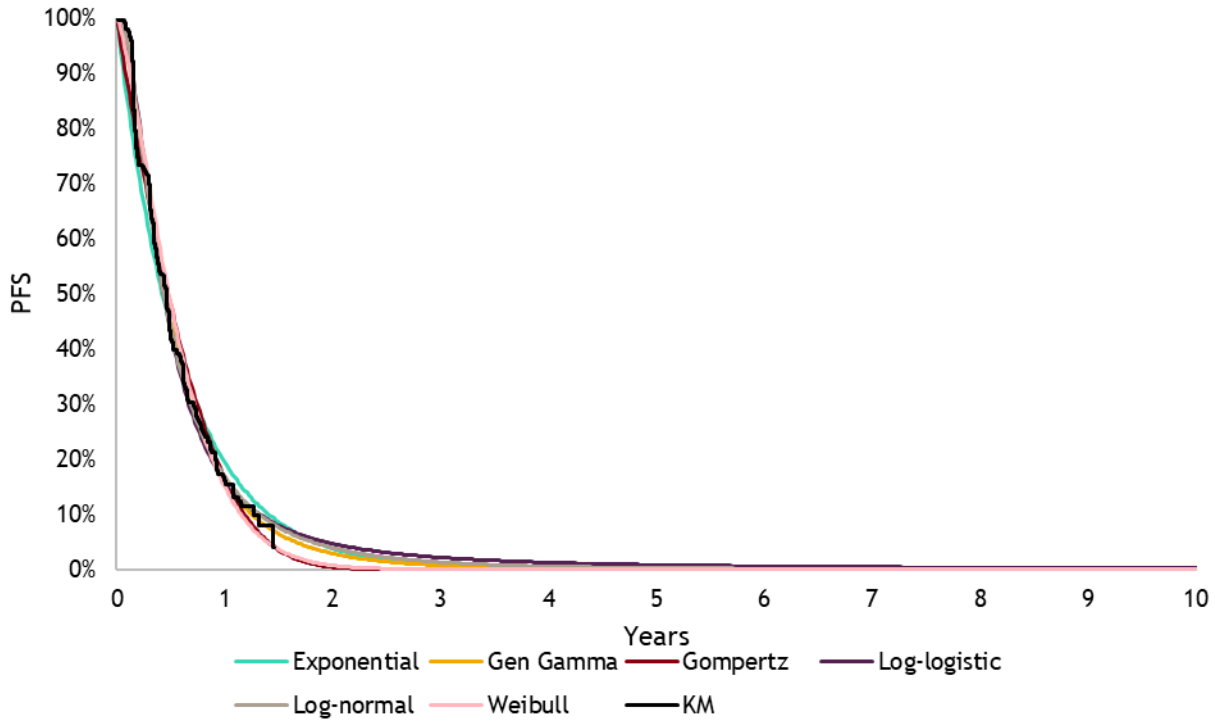
BIC scores, the log-normal and generalised gamma models provided the best fit for the trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil arms, respectively.

**Table 35: Statistical goodness-of-fit scores - PFS**

| Parameterisation | Trifluridine-tipiracil plus bevacizumab | | Trifluridine-tipiracil | |
|---|---|---|---|---|
| | AIC | BIC | AIC | BIC |
| Exponential | 1235.1 | 1238.6 | 1095.1 | 1098.6 |
| Generalised gamma | 1195.9 | 1206.4 | **975.3** | **985.8** |
| Gompertz | 1226.1 | 1233.2 | 1076.5 | 1083.5 |
| Log-logistic | 1196.4 | 1203.4 | 990.4 | 997.4 |
| Log-normal | **1195.3** | **1202.3** | 981.3 | 988.3 |
| Weibull | 1208.5 | 1215.5 | 1035.1 | 1042.2 |

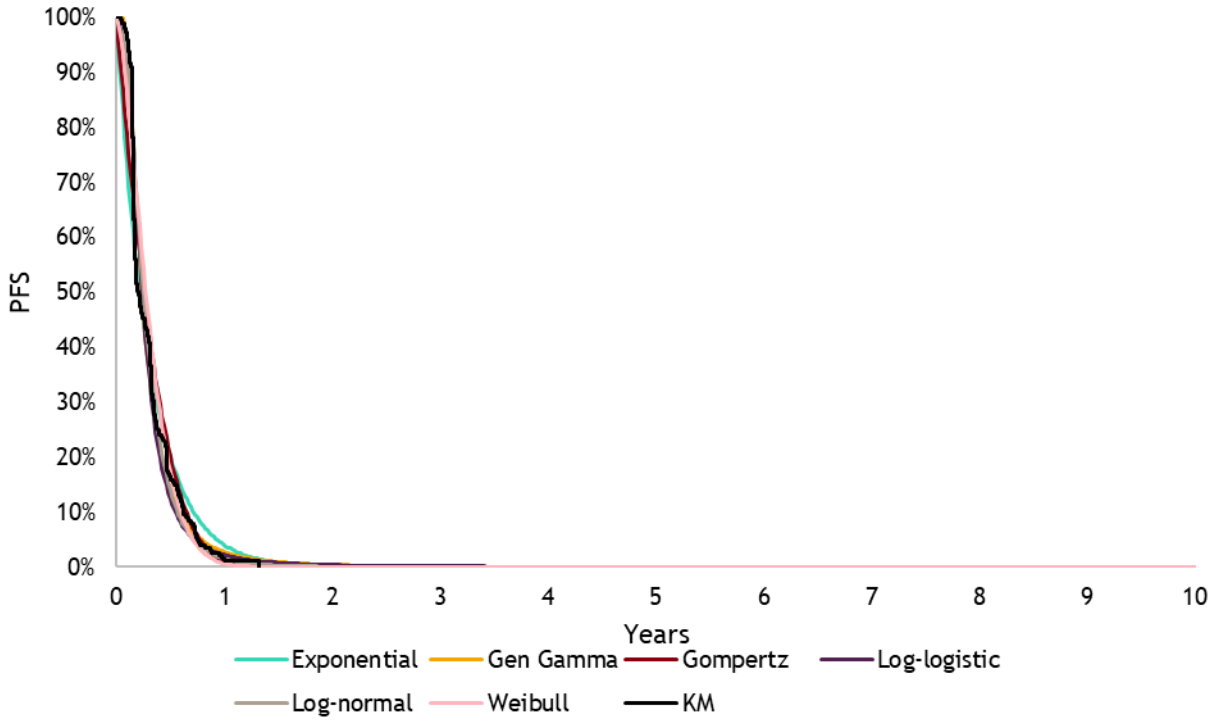
**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival

**Figure 25: Parametric curve fits – Trifluridine-tipiracil plus bevacizumab - PFS**




**Key:** KM, Kaplan-Meier; PFS, progression-free survival

**Figure 26: Parametric curve fits – Trifluridine-tipiracil - PFS**




**Key:** KM, Kaplan-Meier; PFS, progression-free survival

All the curves appear to fit the data reasonably well, with some minor under- and over- estimating throughout due to 'steps' in the observed data likely caused by the protocol driven assessments of progression in the SUNLIGHT trial. For trifluridine-tipiracil monotherapy, clinical experts expected no patients or less than 0.2% at 2 years, and highlighted log-normal as a potential plausible option.[4] For trifluridine-tipiracil plus bevacizumab, clinicians highlighted log-logistic as a plausible option with log-normal also looking plausible. One clinician highlighted that they would expect a maximum of 2% progression-free at 3-years.[4]

Given that log-normal was the best statistically fitting curve for trifluridine-tipiracil plus bevacizumab, visually fits the data well, and is considered plausible based on clinical opinion (1.3% progression-free at 3 years) this has been chosen for the base case. For the trifluridine-tipiracil arm, all distributions project similar outcomes beyond the observed trial therefore the choice of distribution is likely to have minimal impact on results. For consistency, the same distribution (log-normal) was selected for both treatment arms and this was also chosen as a plausible option by clinical experts. Alternative PSMs are considered in scenario analysis.

For regorafenib and BSC, as with OS, the HR derived from the NMA was applied to the trifluridine-tipiracil plus bevacizumab PFS curve. The HRs used in the base case are presented in Table 36.

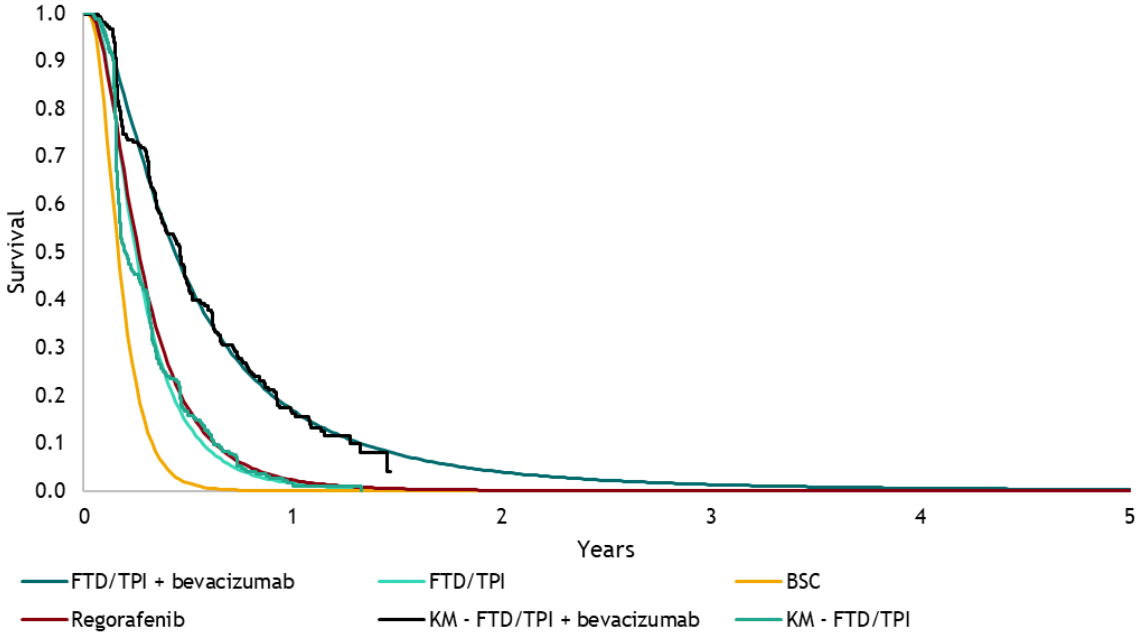
**Table 36: NMA results used in the base case – random-effects – PFS**

| Comparator | HR | 95% CrI |
|---|---|---|
| BSC | 0.20 | 0.13 – 0.31 |
| Regorafenib | 0.47 | 0.29 – 0.82 |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis

A summary of the base case PFS efficacy for all treatments is presented in Figure 27. Similar to OS, PFS outcomes for trifluridine-tipiracil and regorafenib appear similar (which is aligned with clinical opinion and expectations based on prior technology appraisals).[4,45]

**Figure 27: PFS base case summary**



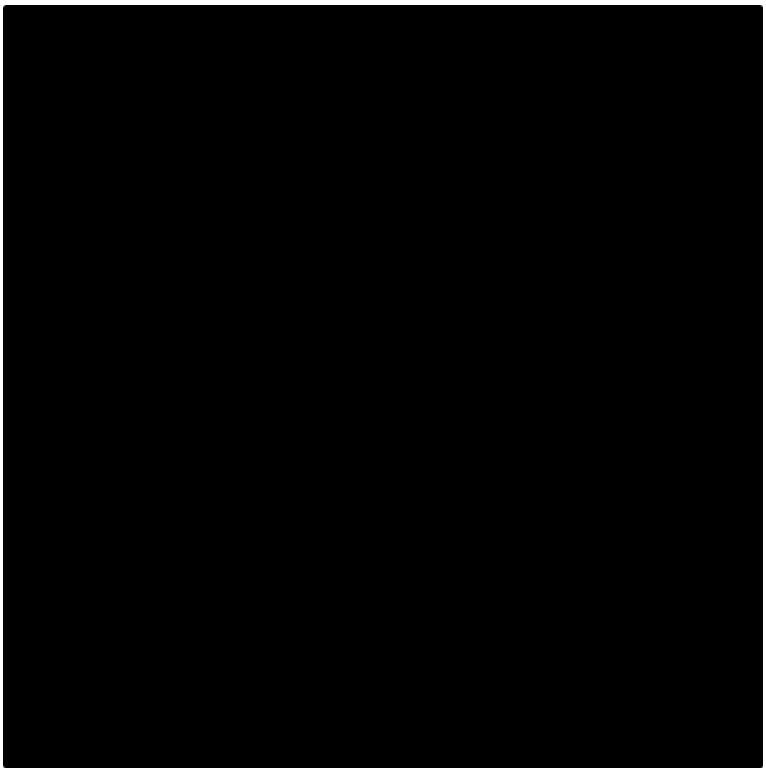

**Key:** BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; KM, Kaplan-Meier; PFS, progression-free survival

#### *B.3.3.2.3 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 trifluridine-tipiracil plus

bevacizumab and trifluridine-tipiracil monotherapy. A summary of the ToT data from SUNLIGHT is provided below in Figure 28.

**Figure 28: SUNLIGHT – Kaplan-Meier – ToT**



**Key:** BEV, bevacizumab; LON, Lonsurf (trifluridine-tipiracil); TT_disc, time to treatment discontinuation; ToT, time on treatment

As patients could stop bevacizumab treatment before trifluridine-tipiracil, to ensure that the treatments are costed accurately and appropriately, the trifluridine-tipiracil plus bevacizumab arm has been separated and all curves have been modelled independently. As such, no LCHP or Q-Q plots have been produced to assess PH or AFT.

The statistical goodness-of-fit of all fitted PSMs is provided in Table 37. Based on the AIC and BIC scores, the Weibull model provided the best fit for the intervention combination treatments and generalised gamma and log-normal were the best fitting for trifluridine-tipiracil. However all models were visually compared in order to select the base case extrapolation (Figure 29, Figure 30 and Figure 31).

**Table 37: Statistical goodness-of-fit scores - ToT**

| Parameterisation | Trifluridine-tipiracil (trifluridine-tipiracil + bevacizumab) | | Bevacizumab (Trifluridine-tipiracil + bevacizumab) | | Trifluridine-tipiracil | |
|---|---|---|---|---|---|---|
| | AIC | BIC | AIC | BIC | AIC | BIC |
| Exponential | 1385.7 | 1389.2 | 1375.8 | 1379.3 | 1099.2 | 1102.7 |
| Generalised gamma | 1339.0 | 1349.5 | **1331.1** | 1341.6 | **984.3** | 994.9 |
| Gompertz | 1348.9 | 1355.9 | 1343.3 | 1350.3 | 1076.5 | 1083.5 |
| Log-logistic | 1359.6 | 1366.6 | 1349.2 | 1356.2 | 997.2 | 1004.2 |
| Log-normal | 1353.8 | 1360.8 | 1343.8 | **1350.8** | 987.1 | **994.1** |
| Weibull | **1338.5** | **1345.6** | 1331.7 | 1338.7 | 1035.9 | 1042.9 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment

**Figure 29: Parametric curve fits – Trifluridine-tipiracil (trifluridine-tipiracil plus bevacizumab) – ToT**

**Key:** KM, Kaplan-Meier; ToT, time on treatment



**Figure 30: Parametric curve fits – bevacizumab (Trifluridine-tipiracil plus bevacizumab) – ToT**

**Key:** KM, Kaplan-Meier; ToT, time on treatment

**Figure 31: Parametric curve fits – Trifluridine-tipiracil – ToT**

**Key:** KM, Kaplan-Meier; ToT, time on treatment



Given the maturity of the data, very little extrapolation is required therefore curves which closely match the observed data have only been considered. For trifluridine-tipiracil and bevacizumab in the intervention arm, the generalised gamma, Gompertz and Weibull curves are the closest to the observed data. As Weibull was also the best statistically fitting, this has been chosen for the base case for both trifluridine-tipiracil and bevacizumab. For trifluridine-tipiracil monotherapy, all curves with the exception of exponential closely match the observed data. As generalised gamma is statistically the best fitting according to AIC and BIC combined, this has been chosen for the base case.

The NMA could not be performed due to insufficient ToT data for regorafenib. Therefore, two scenarios have been considered to estimate regorafenib ToT. The first approach (applied in the model base case) assumes that regorafenib ToT is equivalent to the regorafenib PFS. This methodology is not only aligned with the regorafenib SmPC which indicates that treatment should be given until progression unless unacceptable toxicity occurs,[65] but has also been considered in previous mCRC appraisals in the absence of ToT data.[45] Despite this, clinical feedback indicated that in real-world practice, it is possible that patients receiving regorafenib may stop treatment prior to disease progression. As such, a second approach is considered in scenario analysis which applies the PFS HR for trifluridine-tipiracil plus bevacizumab vs. regorafenib to the ToT arm (trifluridine-tipiracil in the combination arm - as shown in Figure 29).

#### B.3.3.3 Safety

Adverse events associated with receiving different treatments were included to account for the additional costs incurred due to toxicity. Grade ≥3 adverse events with incidence of greater than 2% in either SUNLIGHT or any of the comparators was included within the economic model. Two percent was selected as this cut-off ensured that all the important adverse events were costed and this approach is in line with previous appraisals in mCRC.[45]

Adverse events for trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy were taken from the SUNLIGHT study. Adverse events for regorafenib

and BSC were based on reported adverse events in TA866 using pooled data from CORRECT and CONCUR.[45]

The incidence of the adverse events used in the base case is summarised in Table 38. A constraint of relying on adverse events from the literature for some comparators, is the limited reporting on certain adverse events, compared to trifluridine-tipiracil with bevacizumab where all adverse events reported from SUNLIGHT can be considered. HRQoL impacts and costs associated with AEs were captured within the economic model with details provided in Section B.3.4.4 and B.3.5.3 respectively.

**Table 38: Grade ≥ 3 incidence of adverse events in ≥2%**

| Adverse event | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | BSC | Regorafenib |
|---|---|---|---|---|
| Abdominal pain | 2.0% | 1.6% | - | - |
| Alanine aminotransferase increased | 2.8% | - | - | - |
| Anaemia | 6.1% | 11.0% | - | 2.20% |
| Anorexia | - | - | 2.20% | 2.50% |
| Aspartate aminotransferase increased | 2.4% | 1.2% | - | - |
| Asthenia | 4.1% | 4.1% | - | - |
| Diarrhoea | 0.8% | 2.4% | 0.60% | 5.70% |
| Fatigue | 1.2% | 3.7% | 4.40% | 8.20% |
| Febrile neutropenia | 0.4% | 2.0% | - | - |
| Hand foot skin reaction | - | - | 0.30% | 16.50% |
| Hepatic failure | - | 2.4% | - | - |
| Hyperbilirubinaemia | 1.6% | 1.2% | 0.90% | 3.00% |
| Hypertension | 5.7% | 1.2% | 1.20% | 8.00% |
| Hypophosphataemia | - | - | 0.30% | 4.40% |
| Intestinal obstruction | 2.8% | 1.6% | - | - |
| Jaundice | 1.6% | 2.0% | - | - |
| Leukopenia | 1.6% | 2.8% | - | - |
| Lipase increased | - | - | 0.60% | 3.50% |
| Malignant neoplasm progression | 2.4% | 4.1% | - | - |
| Mucositis | - | - | 0.19% | 2.40% |
| Neutropenia | 43.1% | 32.1% | - | - |

| Adverse event | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | BSC | Regorafenib |
|---|---|---|---|---|
| Neutrophil count decreased | 8.9% | 5.3% | - | - |
| Pulmonary embolism | 0.8% | 2.0% | - | - |
| Rash | - | - | - | 5.50% |
| Thrombocytopenia | 2.8% | 1.2% | 0.30% | 2.80% |
| Source | SUNLIGHT[2] | SUNLIGHT[2] | TA866[45] | TA866[45] |

**Key**: BSC, best supportive care

## *B.3.4 Measurement and valuation of health effects*

### B.3.4.1 Health-related quality of life data from clinical trials and mapping of EQ-5D-5L to EQ-5D-3L

In the SUNLIGHT trial, the EQ-5D-5L questionnaire was administered to patients to measure health-related quality of life (HRQL). The questionnaires were to be completed within 7 days of randomisation, then day 1 of cycles ≥ 2 prior to any study procedure 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 progression-free with the remaining 304 recorded post-progression. In line with NICE guidance, the EQ-5D-5L responses from the SUNLIGHT trial were 'cross-walked' to EQ-5D-3L responses using the mapping approach developed by Hernández-Alava et al.[66–69] Table 39 presents a summary of the data collected.

**Table 39: Summary of SUNLIGHT utility values by health state (EQ-5D-5L cross-walked to EQ-5D-3L)**

| Health state | Number of patients | Number of observations | Mean (SD) | Median (95% CI) |
|---|---|---|---|---|
| Progression-free | 447 | 1,975 | 0.794 (0.190) | 0.820 (0.246 – 0.989) |
| Progressed | 270 | 304 | 0.703 (0.238) | 0.737 (0.066 – 0.989) |

**Key:** CI, confidence interval; SD, standard deviation

### B.3.4.2 Estimating health-related quality of life data to inform model health states

Mapped EQ-5D-3L utility scores based on progression status were derived using a mixed effects regression model. EQ-5D scores from all available timepoints, including baseline, were included in the regression model as dependent variables.

Treatment arm and progression status were included as independent variables. Two regression models were considered:

1. Utility ~ progression

2. Utility ~ progression + treatment

An overview of the mixed effects regression models are provided in Table 40. The resulting utility values for each health state are presented in Table 41.

**Table 40: Mixed effects regression models**

| Coefficient | Value | SE | p-value |
|---|---|---|---|
| **Model 1** | | | |
| Intercept | 0.681 | 0.013 | 0.000 |
| Progression-free | 0.078 | 0.011 | 0.000 |
| **Model 2** | | | |
| Intercept | 0.659 | 0.016 | 0.000 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.043 | 0.018 | 0.021 |
| Progression-free | 0.077 | 0.011 | 0.000 |

**Key:** SE, standard error

**Table 41: Health state utility values from SUNLIGHT using mixed effects regression models**

| Health state | Trifluridine-tipiracil with bevacizumab | Trifluridine-tipiracil | Overall |
|---|---|---|---|
| Progression-free | 0.779 | 0.737 | 0.759 |
| Progressed | 0.702 | 0.659 | 0.681 |

### B.3.4.3 Health-related quality of life studies

#### *B.3.4.3.1 Literature searches*

A systematic literature review was conducted to identify relevant published HRQL data for advanced or mCRC after two prior chemotherapy regimens.

Searches were conducted on 10th February 2023. Further details of the HRQL systematic literature review are provided in Appendix D.

The review identified 9,590 records. After the removal of duplicate records and irrelevant publication types, 3,879 titles/abstracts were screened, resulting in the identification of 101 reports for full-text review. Of these, 79 reports were excluded. After adding seven reports from conference websites, hand-searching, and client-provided materials, a total of 29 reports describing 18 unique studies were included in the systematic literature review. Of these 18 studies, 11 were randomised control trial, one was a single-arm trial, and six were observational studies.

Of the 18 studies, four reported EQ-5D utility values, two of which reported utility values associated with health states relevant to the model structure; study 20020408 and Stein et al 2014.[70,71]

Study 20020408 compared panitumumab with BSC in patients with KRAS wild-type mCRC. In this study EQ-5D utility values for three health states were estimated; toxicity while experiencing an adverse event (TOX), prior to disease progression without adverse events (TWiST) and relapse on or after date of disease progression (REL).[71] Given the study considered panitmumab and was not wholly aligned with the health state definitions considered as part of the decision problem for this appraisal, these values have not been incorporated into the cost-effectiveness model.

Stein et al, 2014 reported a cross sectional study of patients with mCRC at second-line pre and post-progression using the EQ-5D-3L instrument from five hospitals in the Netherlands and UK.[70] Mean utility scores were 0.741 and 0.731 for pre- and post- progression, respectively. Given that the utilities are specifically for the second-line population, these values have not been incorporated into the cost-effectiveness model.

#### *B.3.4.3.2 Previous appraisals*

As well as consideration of utility values reported in the literature, health state utility values reported in prior mCRC NICE appraisals (specifically TA405 and TA866) were also assessed for inclusion within the economic model.[44,45]

In the prior NICE appraisal for trifluridine-tipiracil monotherapy for patients previously treated with mCRC (TA405)[44], HRQL values were not collected in the pivotal

RECOURSE study. Therefore, health state utility values were estimated from the average of utilities in the CORRECT[50] study and TA176 (cetuximab for first-line mCRC – now TA439)[40]. In the regorafenib mCRC submission (TA866)[45], utility values were informed by EQ-5D-3L values pooled from the CORRECT[50] and CONCUR[49] clinical studies. Given the impact of AEs is accounted for separately within the economic model through the application of disutilities (see Section B.3.4.4), and for simplicity, the scenario analysis assumes all arms are equivalent to the trifluridine-tipiracil arm.

A summary of the utility values reported in the literature and considered in scenario analysis within the cost-effectiveness model are presented in Table 42.

**Table 42: Summary of literature utility values**

| Source | Treatment | Progression-free | Progressed |
|---|---|---|---|
| TA405[44] | Trifluridine-tipiracil | 0.73 | 0.64 |
| TA866[45] | Regorafenib/ trifluridine-tipiracil/BSC | 0.72 | 0.59 |

**Key:** BSC, best supportive care

### B.3.4.4 Adverse reactions

The impact of adverse events on HRQL was included in the cost-effectiveness model. The disutility values were identified from published literature.[72–74] The impact of adverse events on patient utility was applied as a one-off QALY loss in the first model cycle and based on the expected duration of each adverse event (the data for which were sourced from the SUNLIGHT study). When an adverse event duration could not be estimated from SUNLIGHT, the duration was assumed to be the mean of the available duration estimates from SUNLIGHT. Table 43 presents the adverse event disutilities and durations used in the cost-effectiveness model.

**Table 43: Disutilities and durations for adverse events**

| Adverse event | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|
| Abdominal pain | -0.0468 | 15.6 | Assumed same as diarrhoea | SUNLIGHT |
| Alanine aminotransferase increased | -0.08973 | 26.7 | Assumed equal to neutropenia | SUNLIGHT |

| Adverse event | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|
| Anaemia | -0.0209 | 118.8 | Sullivan et al 2006[72] | SUNLIGHT |
| Anorexia | -0.0468 | 11.8 | Assumed same as diarrhoea | Average of all AE in SUNLIGHT |
| Aspartate aminotransferase increased | -0.08973 | 14.0 | Assumed equal to neutropenia | SUNLIGHT |
| Asthenia | -0.07346 | 27.6 | Assumed equal to fatigue | SUNLIGHT |
| Diarrhoea | -0.0468 | 31.9 | Nafees et al, 2008[73] | SUNLIGHT |
| Fatigue | -0.07346 | 6.3 | Nafees et al, 2008[73] | SUNLIGHT |
| Febrile neutropenia | -0.15 | 16.2 | Lloyd et al, 2006[74] | SUNLIGHT |
| Hand foot skin reaction | -0.116 | 11.8 | Lloyd et al, 2006[74] | Average of all AE in SUNLIGHT |
| Hepatic failure | -0.0567 | 7.3 | Sullivan et al 2006[72] | SUNLIGHT |
| Hyperbilirubinaemia | -0.08973 | 39.0 | Assumed equal to neutropenia | SUNLIGHT |
| Hypertension | -0.025 | 21.1 | Sullivan et al 2006[72] | SUNLIGHT |
| Hypophosphataemia | -0.0359 | 11.8 | Sullivan et al 2006[72] | Average of all AE in SUNLIGHT |
| Intestinal obstruction | -0.0193 | 9.2 | Sullivan et al 2006[72] | SUNLIGHT |
| Jaundice | -0.07346 | 16.5 | Assumed equal to fatigue | SUNLIGHT |
| Leukopenia | -0.08973 | 20.8 | Assumed equal to neutropenia | SUNLIGHT |
| Lipase increased | -0.08973 | 11.8 | Assumed equal to neutropenia | Average of all AE in SUNLIGHT |
| Malignant neoplasm progression | -0.069 | 9.9 | Assumed same as pain (Doyle et al, 2008)[75] | SUNLIGHT |

| Adverse event | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|
| Mucositis | -0.03248 | 11.8 | Assumed same as rash | Average of all AE in SUNLIGHT |
| Neutropenia | -0.08973 | 11.8 | Nafees et al, 2008[73] | SUNLIGHT |
| Neutrophil count decreased | -0.08973 | 14.6 | Assumed equal to neutropenia | SUNLIGHT |
| Pulmonary embolism | -0.186 | 70.7 | Hunter et al, 2015[76] | SUNLIGHT |
| Rash | -0.03248 | 11.8 | Nafees et al, 2008[73] | Average of all AE in SUNLIGHT |
| Thrombocytopenia | -0.08973 | 34.6 | Assumed equal to neutropenia | SUNLIGHT |

**Key:** AE, adverse event

The total disutility per treatment arm is provided in Table 44. Scenario analysis considers the impact on results when disutilities associated with AEs are not applied.

**Table 44: Disutilities applied for AEs**

| Treatment arm | Disutility applied |
|---|---|
| Trifluridine-tipiracil plus bevacizumab | 0.00356 |
| Trifluridine-tipiracil | 0.00374 |
| BSC | 0.00028 |
| Regorafenib | 0.00201 |

**Key:** AE, adverse event; BSC, best supportive care

### B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

For the model base case, utilities derived from the SUNLIGHT study have been used directly to inform treatment specific utility values for the 'progression-free' and 'progressed disease' health states (see Section B.3.4.2) for trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil monotherapy. The values derived, are based directly on the relevant population of interest and utilise data available which is aligned with the NICE reference case (EQ-5D-5L data which has been cross-walked to the EQ-5D-3L). Treatment specific utilities were considered appropriate as clinical advice to the company indicated that HRQL would likely be improved by the combination regimen over the other available treatments (reflected in the data collected in SUNLIGHT).

It is assumed that regorafenib and BSC have the same health state utilities values as the trifluridine-tipiracil monotherapy arm. Although a simplifying assumption, this seems appropriate given the similarity in outcomes (OS and PFS; see section B.3.3.2) between regorafenib and trifluridine-tipiracil, and on account for impacts associated with AEs being captured separately.

Scenario analysis explores the application of pooled utility values from the SUNLIGHT trial (assuming the same health state utility per treatment arm), as well as the impact of considering utility values applied in previous technology appraisals (TA866 and TA405).[44,45]

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara and Brazier, 2010.[77] The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Table 45 summarises the utility values included within the cost-effectiveness analysis base case.

**Table 45: Summary of utility values for cost-effectiveness analysis**

| State | Treatment | Utility value | 95% confidence interval | Reference in submission | Justification |
|---|---|---|---|---|---|
| Base case | | | | | |
| Progression-free: (SUNLIGHT) | Trifluridine-tipiracil + bevacizumab | 0.779 | 0.746 - 0.813 | B.3.4.2 | Derived from SUNLIGHT study |
| | Trifluridine-tipiracil | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| | Regorafenib | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| | BSC | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| Progressed disease (SUNLIGHT) | Trifluridine-tipiracil + bevacizumab | 0.702 | 0.662 - 0.742 | B.3.4.2 | |
| | Trifluridine-tipiracil | 0.659 | 0.628 - 0.691 | B.3.4.2 | |
| | Regorafenib | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| | BSC | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| **Scenario analysis 1** | | | | | |
| Progression-free: (SUNLIGHT pooled) | All | 0.759 | 0.734 - 0.785 | B.3.4.2 | Exploration of uncertainty using pooled treatment utilities from SUNLIGHT trial |
| Progressed disease (SUNLIGHT pooled) | All | 0.681 | 0.655 - 0.707 | B.3.4.2 | |
| **Scenario analysis 2** | | | | | |
| Progression-free: (TA866)[45] | All | 0.72 | 0.71 - 0.73 | B.3.4.3.2 | Exploration of uncertainty using previous TAs |
| Progressed disease (TA866)[45] | All | 0.59 | 0.56 - 0.62 | B.3.4.3.2 | |
| **Scenario analysis 3** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Progression-free: (TA405)[44] | All | 0.73 | 0.71-0.75 | B.3.4.3.2 | Exploration of uncertainty using previous TAs |
| Progressed disease (TA405)[44] | All | 0.64 | 0.62-0.66 | B.3.4.3.2 | |

**Key:** BSC, best supportive care; TA, technology appraisal

## *B.3.5 Cost and healthcare resource use identification, measurement and valuation*

A systematic literature review was conducted to identify cost and resource use studies for previously treated mCRC in the third-line setting. Full details of the review are presented in Appendix I.

### B.3.5.1 Intervention and comparators' costs and resource use

#### *B.3.5.1.1 Drug acquisition costs*

***Unit drug costs***

The unit drug costs for each treatment included within the cost-effectiveness model and its source are summarised in Table 46. The unit costs have been sourced from the British National Formulary (BNF).[78] There is an approved PAS for trifluridine-tipiracil of [redacted] which in incorporated throughout the results section (B.3.10). In UK clinical practice, Servier are aware that the list price for bevacizumab is likely to vary due to the availability of biosimilars on the market and loss of exclusivity. Regorafenib may have a patient access scheme, however as this is confidential, no discount is applied throughout the economic analysis.

**Table 46. Unit drug costs of each treatment**

| Drug | Dose (mg) | Qty | Unit cost (£) (with PAS) | Source |
|---|---|---|---|---|
| Trifluridine-tipiracil | 15 mg | 20 | 500.00 ([redacted]) | BNF – Lonsurf[79] |
| | 15 mg | 60 | 1,500.00 ([redacted]) | |
| | 20 mg | 20 | 666.67 ([redacted]) | |
| | 20 mg | 60 | 2,000.00 ([redacted]) | |
| Bevacizumab | 100 mg | 1 | 205.00 | BNF - Vegzelma[80] |
| | 400 mg | 1 | 810.00 | |
| Regorafenib | 40 mg | 84 | 3,744.00 | BNF - Stivarga[81] |

**Key:** BNF, British National Formulary; eMIT, electronic market information tool; Qty, quantity

***Trifluridine-tipiracil dosing***

The dosing schedule for each treatment was taken from the treatments summary of product characteristics (SmPC). Trifluridine-tipiracil is administered orally at a dose of 35mg/m$^2$ twice daily on days 1 to 5 and 8 to 12 in a 28-day cycle until disease progression or unacceptable toxicity.[62] This dose was administered within the SUNLIGHT trial, and is representative of the anticipated licensed dose for mCRC in combination with bevacizumab.

The licensed dose of trifluridine-tipiracil is based on patient body surface area (BSA), with pack sizes available to cater for all doses. The SmPC for trifluridine-tipiracil provides dosing bands based on BSA, which are presented in Table 47.

The distribution of BSA used in the model base case was derived from a log-normal fit to the BSA distribution in SUNLIGHT.[82] 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 body surface area (BSA) and is shown in Table 47.

**Table 47. Dose calculation according to BSA.**

| BSA (m$^2$) | Dose in mg (2x daily) | Tablets per dose | | Total daily dose (mg) | BSA distribution |
|---|---|---|---|---|---|
| | | 15mg | 20mg | | |
| < 1.07 | 35 | 1 | 1 | 70 | 0.0% |
| 1.07 – 1.22 | 40 | 0 | 2 | 80 | 0.0% |
| 1.23 – 1.37 | 45 | 3 | 0 | 90 | 0.9% |
| 1.38 – 1.52 | 50 | 2 | 1 | 100 | 6.1% |
| 1.53 – 1.68 | 55 | 1 | 2 | 110 | 19.2% |
| 1.69 – 1.83 | 60 | 0 | 3 | 120 | 26.8% |
| 1.84 – 1.98 | 65 | 3 | 1 | 130 | 23.7% |
| 1.99 – 2.14 | 70 | 2 | 2 | 140 | 14.8% |
| 2.15 – 2.29 | 75 | 1 | 3 | 150 | 5.8% |
| ≥ 2.30 | 80 | 0 | 4 | 160 | 2.6% |

**Key:** BSA, body surface area

**Source:** Lonsurf SmPC [62]

***Bevacizumab dosing***

Bevacizumab is given intravenously at 5mg/kg every 2 weeks alongside the oral dose of trifluridine-tipiracil. For bevacizumab patient-level data from SUNLIGHT are

used with the method of moments technique to calculate the average number of vials that would be required to satisfy one administration of treatment.[82] The method of moments first derives a log-normal distribution for the patient weight within the study based upon the mean and standard deviation measured at baseline. It then uses the log-normal distribution to predict what proportion of patients requires 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 combination of the same dose, only the cheapest option was carried forward. An alternative method is included within scenario analysis using the minimum cost per mg for each treatment (i.e., excluding wastage).

***Regorafenib dosing***

Regorafenib is administered orally at 160mg daily for 21-days followed by 7 days rest over the 28-day treatment cycle.[65] Treatment for regorafenib continues as long as benefit is observed or until unacceptable activity. As regorafenib is flat dosed, method of moments is not required, therefore to account for wastage the cost of the pack is accounted for at the start of each 28-day cycle.

***Best supportive care***

BSC can consist of a variety of concomitant treatments, procedures and other palliative care. In line with assumptions made in previous NICE appraisals the costs of BSC are assumed to be captured by resource use and therefore treatment costs are assumed to be £0.[44,45]

***Dose reductions/delays***

In the SUNLIGHT study, dose reductions were allowed for patients with adverse events (up to three dose reductions for trifluridine-tipiracil). In those cases of dose reductions in SUNLIGHT, doses of trifluridine-tipiracil were reduced to from 35 mg/m$^2$ to 30 mg/m$^2$ (level 1), then from 30 mg/m$^2$ to 25 mg/m$^2$ (level 2), then from 25 mg/m$^2$ to 20 mg/m$^2$ (level 3). For bevacizumab, dose reductions due to adverse

events were not recommended with treatment having to either be permanently discontinued or temporarily suspended. If bevacizumab was discontinued, patients could continue with trifluridine-tipiracil alone. To account for dose reductions, missed doses and treatment interruptions, the relative dose intensity (RDI) from SUNLIGHT has been incorporated in the base case. Given the similarity in outcomes, it is assumed that the RDI for regorafenib is the same as trifluridine-tipiracil monotherapy. Use of the CORRECT study to inform regorafenib RDI is considered in scenario analysis. A further scenario is tested which assumes that no dose reductions/delays are experienced in any treatment arm.

Table 48 presents the treatment regimens with the dosing schedules, dose intensity and cost per treatment cycle.

**Table 48. Dosing schedules, and cost per dose for each treatment.**

| Treatment | | Dose | Dose intensity | Cost per dose (£)[a] (with PAS) | Dosing source | Dose intensity source |
|---|---|---|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | 35 mg/m$^2$ twice daily on days 1-5, 8-12 Q4W | 85.00% | 1,766 ([redacted]) | Trifluridine-tipiracil SmPC[62] | SUNLIGHT[2] |
| | Bevacizumab | 5 mg/kg Q2W | 86.90% | 741 | Bevacizumab SmPC[61] | |
| Trifluridine-tipiracil | | 35 mg/m$^2$ twice daily on days 1-5, 8-12 Q4W | 87.25% | 1,812 ([redacted]) | Trifluridine-tipiracil SmPC[62] | |
| Regorafenib | | 160 mg once daily for 21 days Q4W | 87.25% | 3,744[b] | Regorafenib SmPC[65] | Grothey et al, 2013[50] |

**Key:** PAS, patient access scheme; Q2W, every 2 weeks; Q4W, every 4 weeks; SmPC, summary of product characteristics

**Notes:** [a] Including wastage and dose intensity; [b] Cost every 4 weeks



#### *B.3.5.1.2 Administration costs*

Treatment administration costs are based on NHS Cost Collection 21/22 data.[83] The cost of £286.71 (SB12Z - deliver simple parenteral chemotherapy at first attendance) was applied every two weeks for bevacizumab.

For oral therapies, no administrations costs are included as they are assumed to be captured by routine visits in line with assumptions made in prior appraisals.[44,45]

### B.3.5.2 Health state unit costs and resource use

Disease monitoring resource costs are based on resource use estimates used in prior NICE appraisals TA405 and TA886.[44,45]

Based on TA866, for the progression-free health state, patients on oral treatments are assumed to attend an oral chemotherapy outpatient appointment (per 4 weeks). During this appointment they are assumed to receive treatment for the upcoming cycle, undergo routine tests and see a clinician to review their treatment. A third of patients are also assumed to undergo a computerised tomography every 4 weeks. It is assumed that BSC patients do not attend any routine oncologist visits. For patients on IV treatment, the routine monitoring is assumed the same as oral treatments, but they attend a medical oncologist visit every 4 weeks instead of an oral outpatient visit. Based upon the expert opinion of palliative care elicited from TA405, 25% of patients also incur the cost of a health home care visit.

Following progression, routine monitoring is expected to change as patients receive more palliative and home-based care. Patients are assumed to no longer attend outpatient visits and instead receive local care. All treatments are assumed to receive the same post-progression monitoring costs.

Table 49 summarises the frequencies and proportion of patients for each resource use with unit costs presented in Table 50. The unit costs were sourced from National Cost Collection 20/21[83] data or PSSRU 2022.[84] The total cost per model cycle per health state is presented in Table 51.

**Table 49. Disease monitoring resource use per 28-day cycle**

| Resource use | Progression-free | | | Progressed |
|---|---|---|---|---|
| | IV | Oral | BSC | |
| Oral chemotherapy outpatient | - | 100% | - | - |
| Medical oncologist visit | 100% | - | - | |
| GP home consultation | - | - | - | 25% |
| Community nurse specialist visit | - | - | - | 100% |
| Health home visitor | 25% | 25% | 25% | 100% |
| District nurse visit | - | - | - | 100% |
| GP surgery visit | - | - | - | 100% |
| CT scan | 33% | 33% | - | - |

**Key:** BSC, best supportive care; CT, computerised tomography; Freq, frequency; GP, general practitioner; IV, intravenous

**Table 50. Disease monitoring resource use unit costs**

| Resource use | Unit cost (£) | Source |
|---|---|---|
| Oral chemotherapy outpatient | 197.25 | NHS Cost Collection 21/22 - SB11Z - Deliver Exclusively Oral Chemotherapy – outpatient[83] |
| Medical oncologist visit | 205.78 | NHS Cost Collection 21/22 - 370 - Medical oncology - Total outpatient[83] |
| GP home consultation | 89.01 | PSSRU 2022: Calculated based on GP cost per minute (£3.87, without qualifications), assuming out of surgery visit lasting 23 minutes[84] |
| Community nurse specialist visit | 57.00 | PSSRU 2022: Band 6 Nurse Cost per hour (contact assumed to last 1 hour)[84] |
| Health home visitor | 23.00 | PSSRU 2022: Home care worker Cost per hour (contact assumed to last 1 hour)[84] |
| District nurse visit | 46.00 | PSSRU 2022: Band 5 Nurse Cost per hour (contact assumed to last 1 hour)[84] |
| GP surgery visit | 36.00 | PSSRU 2022: GP consultation (Per surgery consultation lasting 9.22 minutes, without qualifications)[84] |
| CT scan | 160.38 | NHS Cost Collection 21/22 - RD26Z - Computerised Tomography Scan of Three Areas, with Contrast - Total HRGs[83] |

**Key:** CT, computerised tomography; Freq, frequency; GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

**Table 51: Total resource use cost per health state**

| Health state | Cost per cycle (£) |
|---|---|
| Progression-free – IV | 66.11 |
| Progression-free – oral | 63.98 |
| Progression-free – BSC | 1.44 |
| Progressed | 46.06 |

**Key:** BSC, best supportive care; IV, intravenous

#### B.3.5.3 Adverse reaction unit costs and resource use

Unit costs for the management of treatment-related grade 3+ AEs occurring in ≥2% of patients (Section B.3.3.3) are presented in Table 52. Unit costs were sourced from the NHS National Cost Collection (2020/21).[83]

Consistent with the approach for modelling adverse event utility decrements (Section B.3.4.4), a one-off adverse event management cost was calculated and applied in the first model cycle. Table 53 reports the total AE cost per treatment arm.

**Table 52: Adverse event management costs**

| Adverse event | Cost per event (£) | Cost code |
|---|---|---|
| Abdominal pain | 204.36 | NHS cost collection 2020/2021) 191 - Pain management - Total outpatient attendance |
| Alanine aminotransferase increased | 2,214.32 | NHS cost collection 2020/2021) Weighted average: GC17 C - K - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions - Total HRGs |
| Anaemia | 703.48 | NHS cost collection 2020/2021) Weighted average: SA04H-L - Iron Deficiency Anaemia - Total HRGs |
| Anorexia | 152.96 | NHS cost collection 2020/2021) 300 - General medicine - Total outpatient attendance |
| Aspartate aminotransferase increased | 2,214.32 | NHS cost collection 2020/2021) Weighted average: GC17 C - K - Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Multiple Interventions - Total HRGs |
| Asthenia | 703.48 | NHS cost collection 2020/2021) Weighted average: SA04H-L - Iron Deficiency Anaemia - Total HRGs |
| Diarrhoea | 1,746.82 | NHS cost collection 2020/2021) Weighted average: FD01 A-J - Gastrointestinal Infections without Interventions - Total HRGs |
| Fatigue | 703.48 | NHS cost collection 2020/2021) Weighted average: SA04H-L - Iron Deficiency Anaemia - Total HRGs |
| Febrile neutropenia | 3,676.55 | NHS cost collection 2020/2021) Weighted average: SA35A-E - Agranulocytosis - Non-elective long stay |
| Hand foot skin reaction | 1,581.81 | NHS cost collection 2020/2021) J Weighted average: D07E - K - Skin disorders without interventions - Total HRGs |

| Adverse event | Cost per event (£) | Cost code |
|---|---|---|
| Hepatic failure | 2,262.30 | NHS cost collection 2020/2021) Weighted average: GC01E-F - Liver Failure Disorders without Interventions - Total HRGs |
| Hyperbilirubinaemia | 152.96 | NHS cost collection 2020/2021) 300 - General medicine - Total outpatient attendance |
| Hypertension | 770.10 | NHS cost collection 2020/2021) EB04Z - Hypertension - Total HRGs |
| Hypophosphataemia | 152.96 | NHS cost collection 2020/2021) 300 - General medicine - Total outpatient attendance |
| Intestinal obstruction | 169.77 | NHS cost collection 2020/2021) 106 - Upper Gastrointestinal Surgery - Total outpatient |
| Jaundice | 703.48 | NHS cost collection 2020/2021) Weighted average: SA04H-L - Iron Deficiency Anaemia - Total HRGs |
| Leukopenia | 627.97 | NHS cost collection 2020/2021) Weighted average: SA35A-E - Agranulocytosis - Non-elective short stay |
| Lipase increased | 205.78 | NHS cost collection 2020/2021) 370 - Medical oncology - Total outpatient |
| Malignant neoplasm progression | 220.87 | NHS cost collection 2020/2021) 371 - Medical oncology - Consultant led |
| Mucositis | 152.96 | NHS cost collection 2020/2021) 300 - General medicine - Total outpatient attendance |
| Neutropenia | 627.97 | NHS cost collection 2020/2021) Weighted average: SA35A-E - Agranulocytosis - Non-elective short stay |
| Neutrophil count decreased | 627.97 | NHS cost collection 2020/2021) Weighted average: SA35A-E - Agranulocytosis - Non-elective short stay |
| Pulmonary embolism | 1905.92 | NHS cost collection 2020/2021) Weighted average: DZ09J-Q - Pulmonary Embolus without Interventions - Total HRGs |
| Rash | 1,581.81 | NHS cost collection 2020/2021) Weighted average: JD07E - K - Skin disorders without interventions - Total HRGs |
| Thrombocytopenia | 627.97 | NHS cost collection 2020/2021) Weighted average: SA35A-E - Agranulocytosis - Non-elective short stay |

**Table 53: Total adverse event cost**

| Treatment | Cost (£) |
|---|---|

| | |
|---|---|
| Trifluridine-tipiracil plus bevacizumab | 668.68 |
| Trifluridine-tipiracil | 670.79 |
| BSC | 64.03 |
| Regorafenib | 625.93 |

**Key:** BSC, best supportive care

### B.3.5.4 Miscellaneous unit costs and resource use

#### *B.3.5.4.1 Subsequent treatments*

Subsequent treatments were included in the model as an average cost per patient, which is applied as a one-off cost to patients leaving the progression-free state.

Patients were assumed to receive subsequent treatments for a mean duration of 2 months, which is line with clinical opinion received[4] and used in a previous mCRC in NICE submission (TA668).[28]

In the base case, the distribution of subsequent treatments is based on the subsequent treatments received in the SUNLIGHT study to align costs with efficacy used in the cost-effectiveness analysis. In the SUNLIGHT study, 110 patients on the trifluridine-tipiracil with bevacizumab arm (61.8% of those who progressed), and 114 patients on the trifluridine-tipiracil monotherapy arm (55.3% of those who progressed) received at least one subsequent treatment.

To estimate the distribution of subsequent treatments received, records pertaining to the treatment combinations received by patients after their initial treatment in the SUNLIGHT trial to the end of follow-up were analysed. It was assumed that individual treatments recorded at the same visit were a combination treatment. Duplicate entries of the same drug at different visits were assumed to be a continuation of the provision given at previous visits and were therefore not included in the dataset estimating the subsequent treatments given to patients. As there were many variations of treatments and regimen combinations received in the clinical study, further steps were taken to create a concise number of subsequent treatments to cost within the economic model which are described in Appendix O.

Final subsequent treatment distributions from SUNLIGHT are presented in Table 54.

**Table 54: Subsequent treatment distributions from SUNLIGHT**

| Subsequent treatment | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | Pooled |
|---|---|---|---|
| Regorafenib | 25.8% | 35.5% | 30.9% |
| Capecitabine | 8.6% | 6.7% | 7.6% |
| Doublet chemotherapy | 18.8% | 17.0% | 17.8% |
| Triplet chemotherapy | 6.3% | 3.0% | 4.5% |
| Fruquintinib | 3.1% | 2.2% | 2.6% |
| Trifluridine-tipiracil | 3.1% | 1.5% | 2.3% |
| Irinotecan | 2.3% | 1.5% | 1.9% |
| Nivolumab | 1.6% | 1.5% | 1.5% |
| Bevacizumab+ doublet chemotherapy | 11.7% | 7.4% | 9.4% |
| Bevacizumab + triplet chemotherapy | 2.3% | 3.0% | 2.7% |
| Cetuximab + doublet chemotherapy | 2.3% | 2.2% | 2.3% |
| Cetuximab+ triplet chemotherapy | 1.6% | 0.7% | 1.1% |
| Ramucirumab + doublet chemotherapy | 1.6% | 0.0% | 0.7% |
| Aflibercept + doublet chemotherapy | 1.6% | 2.2% | 1.9% |
| Panitumumab + doublet chemotherapy | 3.1% | 3.7% | 3.4% |
| Capecitabine + oxaliplatin | 4.7% | 11.1% | 8.1% |
| Bevacizumab + capecitabine | 1.6% | 0.8% | 1.1% |

Due to the uncertainty of which subsequent treatments patients are likely to receive after their third-line treatment, the base case assumes that the same distribution of subsequent treatments using the pooled SUNLIGHT data is used for all active treatments. For BSC, no further treatment is expected and therefore the cost of subsequent treatment is zero.

To explore uncertainty, alternative options are explored in scenario analysis. The first scenario assumes that no patients receive subsequent therapy, which is what the company assumed in the TA866 regorafenib NICE submission.[45] This assumption was based on clinical advice given to the company that only 10% of patients would have post-progression treatment after regorafenib or trifluridine-tipiracil. However, the committee concluded that subsequent treatments should be included in the model, but that it is not likely to have a large impact on cost-effectiveness. The second scenario uses the treatment specific SUNLIGHT distributions. In this

scenario, regorafenib is assumed to have the same distribution of subsequent treatments as trifluridine-tipiracil.

The final scenarios are based on what would be given in UK clinical practice. The six clinicians consulted as part of the submission process were asked what treatments would be given at fourth-line.[4] There was a general consensus that patients would receive either regorafenib or trifluridine-tipiracil monotherapy and BSC. Re-challenge would not occur, but if patients were fit enough on regorafenib, then patients could be treated with trifluridine-tipiracil, and vice versa. There was concern over treating bevacizumab after regorafenib due to similar mechanisms of action so it was more likely that trifluridine-tipiracil would be given alone. There were differing opinions on how many patients would be expected to receive subsequent treatment at fourth-line. The majority of clinicians expected that fewer patients on the trifluridine-tipiracil plus bevacizumab arm would receive subsequent treatments (approx. 20% versus 50% on the other treatment arms) as it is unlikely patients would be treated with a less effective drug at the next line. One clinician expected there would be more receiving subsequent treatment after trifluridine-tipiracil plus bevacizumab and another estimated between 30-50% across all treatment arms.

Based on the above, the ‘UK practice’ scenarios assume that all patients receiving subsequent treatment after trifluridine-tipiracil plus bevacizumab or trifluridine-tipiracil would receive regorafenib, and all those receiving treatment after regorafenib would receive trifluridine-tipiracil. One scenario assumes that 20% of patients on the trifluridine-tipiracil plus bevacizumab arm would receive treatment, and 50% of the trifluridine-tipiracil and regorafenib arm would receive treatment. The other scenario assumes that 40% of patients receive treatment on all treatment arms.

For the subsequent treatment costs, doublet chemotherapy was assumed to be FOLFOX, and triplet chemotherapy assumed to be FOLFOXIRI. Drugs in combination with ramucirumab, aflibercept and panitumumab, were costed as FOLFIRI.[85] Fruquintinib does not yet have a UK price, therefore the US-based price was used and converted to Great British Pounds. The unit costs for treatments not included in Section B.3.5.1.1 are presented in Appendix K, and the respective doses of the treatment regimens are presented in the Appendix O Total costs over the 2

months duration including administration are presented in Table 55. The resulting total cost per treatment arm are presented in Table 56.

**Table 55: Total weekly subsequent treatment costs**

| Subsequent treatment | Total cost (£) [a] |
|---|---|
| Regorafenib | 8,140 |
| Capecitabine | 71 |
| Doublet Chemotherapy (FOLFOX) | 3,941 |
| Triplet Chemotherapy (FOLFOXIRI) | 4,013 |
| Fruquintinib | 667 |
| Trifluridine-tipiracil | 3,621 |
| Irinotecan | 926 |
| Nivolumab | 12,695 |
| Bevacizumab+ doublet chemotherapy (FOLFOX) | 7,199 |
| Bevacizumab + triplet chemotherapy (FOLFOXIRI) | 7,272 |
| Cetuximab + doublet chemotherapy (FOLFOX) | 13,581 |
| Cetuximab+ triplet chemotherapy (FOLFOXIRI) | 13,653 |
| Ramucirumab + doublet chemotherapy (FOLFIRI) | 16,795 |
| Aflibercept + doublet chemotherapy (FOLFIRI) | 7,728 |
| Panitumumab + doublet chemotherapy (FOLFIRI) | 11,246 |
| Capecitabine + oxaliplatin | 9895 |
| Bevacizumab + capecitabine | 966 |

**Key:** FOLFIRI, fluorouracil plus irinotecan plus leucovorin; FOLFOX, fluorouracil plus oxaliplatin plus leucovorin; FOLFOXIRI, fluorouracil plus oxaliplatin plus irinotecan plus leucovorin

**Note:** [a] Total cost over the two month duration

**Table 56: Total subsequent treatment cost**

| Treatment | Cost (£) |
|---|---|
| Trifluridine-tipiracil plus bevacizumab | 3,342.59 |
| Trifluridine-tipiracil | 3,342.59 |
| BSC | 0.00 |
| Regorafenib | 3,342.59 |

**Key:** BSC, best supportive care

#### *B.3.5.4.2 Terminal care*

A one-off terminal care cost was applied within the economic model which was assumed to cover costs of supporting patients in a palliative (end of life) stage before death. The end of life cost was based on Round et al (2015).[86]

Round et al was a modelling study estimating the cost of caring for cancer patients at the end of their life. The study reports a mean cost among four cancer types (breast, colorectal, lung and prostate). The total end of life health care cost associated with CRC health, social and charity care was reported as £6,910 which was then uplifted to 2022 prices using the PSSRU inflation indices (£7,748).[84]

### *B.3.6 Severity*

Due to the severity of mCRC, patients suffering from the disease face a poor prognosis with substantially reduced life expectancy versus that of the general population (and with poorer HRQL). In line with the new NICE methods, the severity of the condition was determined by estimating the proportional and absolute QALY shortfall. These estimates were obtained using the R-Shiny tool developed by Schneider et al., (2021).[87] The published QALY shortfall tool provides five methods for estimating population quality-adjusted life expectancy. The reference cases uses the Office of National Statistics data (ONS) with an EQ-5D-3L value set and Health Survey for England data from 2014.[88–90] Further descriptions of the methods can be found within the published tool.[87]

A summary of features used to estimate lifetime QALYs without the disease are based on patient baseline characteristics from SUNLIGHT and are presented in Table 57.

**Table 57: Summary features of QALY shortfall analysis**

| Factor | Value [a] | Reference to section in submission |
|---|---|---|
| Sex distribution | 48% | Section B.3.3.1 (Table 32) |
| Starting age | 62 | |

**Key:** QALYs, quality-adjusted life years

**Notes:** [a] Rounded to 0 decimal places per the requirements of the published QALY shortfall tool

A summary of the health state utility values and base case undiscounted life years for the comparators (trifluridine-tipiracil, regorafenib and BSC) are presented in Table 58.

**Table 58: Summary of health state benefits and utility values for QALY shortfall analysis**

| State | Utility value: mean | Undiscounted life years | | |
|---|---|---|---|---|
| | | Trifluridine-tipiracil | Regorafenib | BSC |
| Progression-free | 0.737 | 0.23 | 0.25 | 0.14 |
| Progressed | 0.659 | 0.39 | 0.32 | 0.28 |

**Key:** BSC, best supportive care; QALYs, quality-adjusted life years

The total remaining discounted QALYs for patients treated with trifluridine-tipiracil, regorafenib or BSC were taken from the cost-effectiveness model 'results' worksheet (and inputted into the QALY shortfall tool to two decimal places).

Using the patient characteristics in Table 57 and the reference case QALY shortfall tool, the estimated total QALYs for the general population (without the disease) is 12.01. For trifluridine-tipiracil, the absolute and QALY shortfalls meet the threshold of a QALY weight of 1.2. For regorafenib and BSC, the QALY shortfalls meet the QALY weight of 1.7 (see Table 58). The severity weighting outcomes are consistent across all alternative sources provided in the QALY shortfall tool.

**Table 59: Summary of QALY shortfall analysis (using Schneider et al 2021 reference case)[87]**

| Expected total QALYs for the general population | Total QALYs that people living with a condition would be expected to have with current treatment | QALY shortfall | QALY weight |
|---|---|---|---|
| 12.01 | Trifluridine-tipiracil: 0.62 | Absolute: 11.39<br>Proportional: 94.84% | X1.2 |
| | Regorafenib: 0.56 | Absolute: 11.45<br>Proportional: 95.34% | X1.7 |
| | BSC: 0.43 | Absolute: 11.58<br>Proportional: 96.42% | X1.7 |

**Key:** BSC, best supportive care; QALYs, quality-adjusted life years

Table 60 presents the QALY shortfall from previous comparator appraisals. TA405 was appraised under the old methods before the severity modifier approach was used. Therefore, the calculations were based on the reported patient characteristics and total discounted QALYs from the committees preferred approach (i.e., the ERG's

base case using the pooled data set).[44] TA866 redacted their QALY results so it is unclear what information was used to estimate the severity calculations. The company estimated a QALY weight of x1.7 for both comparators (trifluridine-tipiracil and BSC), however the committee felt there was too much uncertainty with the trifluridine-tipiracil comparison so would not be able to apply the 1.7 weighting. It is unclear whether the committee applied the 1.2 weighting or no weighting in the final outcomes. For BSC, the committee agreed with the application of a x1.7 severity weighting.

The results from previous comparator appraisals are consistent with the current calculations and supportive of the application of the QALY weightings.[87]

**Table 60: Summary list of QALY shortfall from previous evaluations**

| TA | Expected total QALYs for the general population | Expected total QALYs that people living with a condition would be expected to have with current treatment | QALY shortfall | QALY weight |
|---|---|---|---|---|
| TA405 | Age = 63<br>39% female<br>QALYs = 11.63 | Trifluridine-tipiracil: 0.56 | Absolute: 11.07<br>Proportional: 95.19% | X1.7 |
| | | BSC: 0.41 | Absolute: 11.22<br>Proportional: 96.47% | X1.7 |

**Key:** BSC, best supportive care; QALYs, quality-adjusted life years

Based on the above, the criteria for applying x1.2 QALY weighting for the comparison against trifluridine-tipiracil monotherapy, and x1.7 QALY weighting for the regorafenib and BSC comparisons are met within the context of this appraisal.

### *B.3.7 Uncertainty*

mCRC can have a significant impact on quality of life with few substantial treatment options by the time the patient requires third-line treatment. The SUNLIGHT study provides head-to-head evidence with one of the current treatment options trifluridine-tipiracil monotherapy and demonstrated significant improvement in PFS and OS.[46,47] Previous studies have also demonstrated significant benefit of trifluridine-tipiracil

monotherapy versus placebo suggesting trifluridine-tipiracil in combination with bevacizumab would provide substantial benefit versus placebo (i.e., proxy for BSC).[52] This was shown in a NMA which pulled together the most relevant clinical studies in patients with mCRC who have been previously treated. Despite a lack of head-to-head comparison with regorafenib, the NMA demonstrated a clinical benefit for trifluridine-tipiracil with bevacizumab, and although results from the NMA may have associated uncertainty (typical with the methodology), the outcomes are largely aligned with expectations from the clinical community which show similarity with regorafenib and trifluridine-tipiracil monotherapy.[36]

Uncertainty in the model inputs have been tested through extensive sensitivity analyses which tests the structural and parameter uncertainty associated with trifluridine-tipiracil plus bevacizumab compared to all relevant comparators (trifluridine-tipiracil monotherapy, regorafenib and BSC). Sensitivity analyses are presented throughout Section B.3.11).

## *B.3.8 Managed access proposal*

Not applicable.

## *B.3.9 Summary of base case analysis inputs and assumptions*

### B.3.9.1 Summary of base case analysis inputs

A summary of key inputs from the base case analysis are presented in Table 61.

**Table 61: Summary of variables applied in the economic model**

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| ***Structural parameters*** | | | |
| Time horizon | 15 years | NA (Fixed) | B.3.2.2.1 |
| Cycle length | 7 days | NA (Fixed) | |
| Discount rate - costs | 3.5% | NA (Fixed) | |
| Discount rate - QALYs | 3.5% | NA (Fixed) | |
| Discount rate - LYs | 0 | NA (Fixed) | |
| ***Patient characteristics*** | | | |
| Age | 62 years | 60.69 - 62.67 (Normal) | B.3.3.1 |
| Proportion female | 0.48 | 0.44 - 0.52 (Beta) | |
| Trial-based BSA ($m^2$) | 1.83 | 1.81 - 1.85 (Normal) | |
| Trial-based Weight (kg) | 74 | 72.58 - 75.44 (Normal) | |
| ***Efficacy*** | | | |
| FTD/TPI + bevacizumab OS curve | Log-logistic | Multinormal (using variance/ Covariance matrix) | B.3.3 |
| FTD/TPI + bevacizumab PFS curve | Log-normal | | |
| FTD/TPI + bevacizumab (FTD/TPI) ToT curve | Weibull | | |
| FTP/TPI + bevacizumab (bevacizumab) ToT curve | Weibull | | |
| FTD/TPI + bevacizumab OS curve | Log-logistic | | |
| FTD/TPI + bevacizumab PFS curve | Log-normal | | |
| FTD/TPI + bevacizumab (FTD/TPI) ToT curve | Generalised Gamma | | |
| HR - OS - BSC | 0.42 | 0.27 - 0.64 (Drawn from posterior) | |
| HR - OS - Regorafenib | 0.61 | 0.36 - 1.06 (Drawn from posterior) | |
| HR - PFS - BSC | 0.20 | 0.13 - 0.31 (Drawn from posterior) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| HR - PFS - Regorafenib | 0.47 | 0.29 - 0.82 (Drawn from posterior) | |
| ***Health state utilities*** | | | |
| Intercept | 0.659 | Multinormal (using variance/ Covariance matrix) | B.3.4.2 |
| FTD/TPI + bev | 0.043 | | |
| Progression-free | 0.077 | | |
| ***Drug costs*** | | | |
| FTD/TPI (20 x 15 mg) unit cost | 500 | NA (Fixed) | B.3.5 |
| FTD/TPI (60 x 15 mg) unit cost | 1500 | NA (Fixed) | |
| FTD/TPI (20 x 20 mg) unit cost | 667 | NA (Fixed) | |
| FTD/TPI (60 x 20 mg) unit cost | 2000 | NA (Fixed) | |
| Bevacizumab (1 x 100 mg) unit cost | 205 | NA (Fixed) | |
| Bevacizumab (1 x 400 mg) unit cost | 810 | NA (Fixed) | |
| Panitumumab (1 x 100 mg) unit cost | 379 | NA (Fixed) | |
| Panitumumab (1 x 400 mg) unit cost | 1517 | NA (Fixed) | |
| Irinotecan (1 x 40 mg) unit cost | 11 | 10.32 - 10.84 (Normal) | |
| Irinotecan (1 x 100 mg) unit cost | 13 | 12.68 - 12.99 (Normal) | |
| Irinotecan (1 x 300 mg) unit cost | 29 | 28.38 - 29.54 (Normal) | |
| Irinotecan (1 x 500 mg) unit cost | 26 | 24.31 - 27.01 (Normal) | |
| Regorafenib (84 x 40 mg) unit cost | 3744 | NA (Fixed) | |
| Cetuximab (1 x 100 mg) unit cost | 178 | NA (Fixed) | |
| Cetuximab (1 x 500 mg) unit cost | 891 | NA (Fixed) | |
| Fluorouracil (1 x 1000 mg) unit cost | 3 | 3.24 - 3.31 (Normal) | |
| Fluorouracil (1 x 2500 mg) unit cost | 4 | 4.08 - 4.15 (Normal) | |
| Fluorouracil (1 x 2500 mg) unit cost | 4 | 4.35 - 4.37 (Normal) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Fluorouracil (1 x 500 mg) unit cost | 3 | 3.4 - 3.42 (Normal) | |
| Fluorouracil (10 x 500 mg) unit cost | 64 | 63.64 - 63.76 (Normal) | |
| Fluorouracil (1 x 5000 mg) unit cost | 8 | 7.56 - 7.6 (Normal) | |
| Leucovorin (1 x 100 mg) unit cost | 38 | NA (Fixed) | |
| Leucovorin (1 x 200 mg) unit cost | 92 | NA (Fixed) | |
| Leucovorin (1 x 300 mg) unit cost | 100 | NA (Fixed) | |
| Leucovorin (1 x 50 mg) unit cost | 20 | NA (Fixed) | |
| Oxaliplatin (1 x 100 mg) unit cost | 15 | 14.77 - 15.12 (Normal) | |
| Oxaliplatin (1 x 200 mg) unit cost | 27 | 26.37 - 28.07 (Normal) | |
| Oxaliplatin (1 x 50 mg) unit cost | 20 | 19.97 - 20.87 (Normal) | |
| Capecitabine (60 x 150 mg) unit cost | 9 | 9.23 - 9.31 (Normal) | |
| Capecitabine (60 x 300 mg) unit cost | 12 | 10.72 - 12.47 (Normal) | |
| Capecitabine (120 x 500 mg) unit cost | 26 | 25.6 - 25.74 (Normal) | |
| Aflibercept (1 x 100 mg) unit cost | 296 | NA (Fixed) | |
| Aflibercept (1 x 200 mg) unit cost | 591 | NA (Fixed) | |
| Fruquintinib (21 x 5 mg) unit cost | 307 | NA (Fixed) | |
| Fruquintinib (21 x 1 mg) unit cost | 230 | NA (Fixed) | |
| Ramucirumab (1 x 100 mg) unit cost | 500 | NA (Fixed) | |
| Ramucirumab (1 x 500 mg) unit cost | 2500 | NA (Fixed) | |
| Nivolumab (1 x 100 mg) unit cost | 1097 | NA (Fixed) | |
| Nivolumab (1 x 120 mg) unit cost | 1317 | NA (Fixed) | |
| Nivolumab (1 x 240 mg) unit cost | 2633 | NA (Fixed) | |
| Nivolumab (1 x 40 mg) unit cost | 439 | NA (Fixed) | |
| RDI - FTD/TPI (FTD/TPI + bevacizumab) | 0.85 | 0.55 - 1.01 (Normal) | B.3.5 |



| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| RDI - Bevacizumab (FTD/TPI + bevacizumab) | 0.87 | 0.51 - 1 (Normal) | |
| RDI - FTD/TPI | 0.87 | 0.49 - 1.01 (Normal) | |
| RDI - Regorafenib | 0.87 | 0.7 - 1.04 (Normal) | |
| ***Administration costs*** | | | |
| Administration cost - SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance | 287 | 230.52 - 342.9 (Normal) | B.3.5 |
| ***Resource use frequencies*** | | | |
| Resource use - progression-free - IV - Oral chemotherapy outpatient | 0.00 | 0 - 0 (Normal) | B.3.5 |
| Resource use - progression-free - IV - Medical oncologist visit | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progression-free - IV - GP home consultation | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - IV - Community nurse specialist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - IV - Health home visitor | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progression-free - IV - District nurse visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - IV - GP surgery visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - IV - CT scan | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use % - progression-free - IV - Oral chemotherapy outpatient | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - IV - Medical oncologist visit | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progression-free - IV - GP home consultation | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - IV - Community nurse specialist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - IV - Health home visitor | 0.25 | 0.2 - 0.3 (Beta) | |
| Resource use % - progression-free - IV - District nurse visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - IV - GP surgery visit | 0.00 | 0 - 0 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Resource use % - progression-free - IV - CT scan | 0.33 | 0.27 - 0.4 (Beta) | |
| Resource use - progression-free - oral - Oral chemotherapy outpatient | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progression-free - oral - Medical oncologist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - oral - GP home consultation | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - oral - Community nurse specialist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - oral - Health home visitor | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progression-free - oral - District nurse visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - oral - GP surgery visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - oral - CT scan | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use % - progression-free - oral - Oral chemotherapy outpatient | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progression-free - oral - Medical oncologist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - oral - GP home consultation | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - oral - Community nurse specialist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - oral - Health home visitor | 0.25 | 0.2 - 0.3 (Beta) | |
| Resource use % - progression-free - oral - District nurse visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - oral - GP surgery visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - oral - CT scan | 1.00 | 0.27 - 0.4 (Beta) | |
| Resource use - progression-free - BSC - Oral chemotherapy outpatient | 0.33 | 0 - 0 (Normal) | |
| Resource use - progression-free - BSC - Medical oncologist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - BSC - GP home consultation | 0.00 | 0 - 0 (Normal) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Resource use - progression-free - BSC - Community nurse specialist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - BSC - Health home visitor | 0.00 | 0.2 - 0.3 (Normal) | |
| Resource use - progression-free - BSC - District nurse visit | 0.25 | 0 - 0 (Normal) | |
| Resource use - progression-free - BSC - GP surgery visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progression-free - BSC - CT scan | 0.00 | 0 - 0 (Normal) | |
| Resource use % - progression-free - BSC - Oral chemotherapy outpatient | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - Medical oncologist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - GP home consultation | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - Community nurse specialist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - Health home visitor | 0.00 | 0.2 - 0.3 (Beta) | |
| Resource use % - progression-free - BSC - District nurse visit | 0.25 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - GP surgery visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progression-free - BSC - CT scan | 0.00 | 0 - 0 (Beta) | |
| Resource use - progressed - Oral chemotherapy outpatient | 0.00 | 0 - 0 (Normal) | |
| Resource use - progressed - Medical oncologist visit | 0.00 | 0 - 0 (Normal) | |
| Resource use - progressed - GP home consultation | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progressed - Community nurse specialist visit | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progressed - Health home visitor | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progressed - District nurse visit | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progressed - GP surgery visit | 0.25 | 0.2 - 0.3 (Normal) | |
| Resource use - progressed - CT scan | 0.00 | 0 - 0 (Normal) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Resource use % - progressed - Oral chemotherapy outpatient | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progressed - Medical oncologist visit | 0.00 | 0 - 0 (Beta) | |
| Resource use % - progressed - GP home consultation | 0.25 | 0.2 - 0.3 (Beta) | |
| Resource use % - progressed - Community nurse specialist visit | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progressed - Health home visitor | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progressed - District nurse visit | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progressed - GP surgery visit | 1.00 | 1 - 1 (Beta) | |
| Resource use % - progressed - CT scan | 0.00 | 0 - 0 (Beta) | |
| *Resource use costs* | | | |
| Resource use - unit cost - Oral chemotherapy outpatient | 197.25 | 158.59 - 235.9 (Normal) | |
| Resource use - unit cost - Medical oncologist visit | 205.78 | 165.45 - 246.11 (Normal) | |
| Resource use - unit cost - GP home consultation | 89.01 | 71.56 - 106.46 (Normal) | |
| Resource use - unit cost - Community nurse specialist visit | 57.00 | 45.83 - 68.17 (Normal) | |
| Resource use - unit cost - Health home visitor | 23.00 | 18.49 - 27.51 (Normal) | |
| Resource use - unit cost - District nurse visit | 46.00 | 36.98 - 55.02 (Normal) | |
| Resource use - unit cost - GP surgery visit | 36.00 | 28.94 - 43.06 (Normal) | |
| Resource use - unit cost - CT scan | 160.38 | 128.94 - 191.81 (Normal) | |
| ***AEs*** | | | |
| Adverse events - Abdominal pain - FTD/TPI + bevacizumab | 0.02 | 0.01 - 0.04 (Beta) | B.3.3.3 |
| Adverse events - Alanine aminotransferase increased - FTD/TPI + bevacizumab | 0.03 | 0.01 - 0.05 (Beta) | |
| Adverse events - Anaemia - FTD/TPI + bevacizumab | 0.06 | 0.03 - 0.09 (Beta) | |
| Adverse events - Anorexia - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Aspartate aminotransferase increased - FTD/TPI + bevacizumab | 0.02 | 0.01 - 0.05 (Beta) | |
| Adverse events - Asthenia - FTD/TPI + bevacizumab | 0.04 | 0.02 - 0.07 (Beta) | |
| Adverse events - Diarrhoea - FTD/TPI + bevacizumab | 0.01 | 0 - 0.02 (Beta) | |
| Adverse events - Fatigue - FTD/TPI + bevacizumab | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Febrile neutropenia - FTD/TPI + bevacizumab | 0.00 | 0 - 0.01 (Beta) | |
| Adverse events - Hand foot skin reaction - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hepatic failure - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hyperbilirubinaemia - FTD/TPI + bevacizumab | 0.02 | 0 - 0.04 (Beta) | |
| Adverse events - Hypertension - FTD/TPI + bevacizumab | 0.06 | 0.03 - 0.09 (Beta) | |
| Adverse events - Hypophosphataemia - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Intestinal obstruction - FTD/TPI + bevacizumab | 0.03 | 0.01 - 0.05 (Beta) | |
| Adverse events - Jaundice - FTD/TPI + bevacizumab | 0.02 | 0 - 0.04 (Beta) | |
| Adverse events - Leukopenia - FTD/TPI + bevacizumab | 0.02 | 0 - 0.04 (Beta) | |
| Adverse events - Lipase increased - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Malignant neoplasm progression - FTD/TPI + bevacizumab | 0.02 | 0.01 - 0.05 (Beta) | |
| Adverse events - Mucositis - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Neutropenia - FTD/TPI + bevacizumab | 0.43 | 0.37 - 0.49 (Beta) | |
| Adverse events - Neutrophil count decreased - FTD/TPI + bevacizumab | 0.09 | 0.06 - 0.13 (Beta) | |
| Adverse events - Pulmonary embolism - FTD/TPI + bevacizumab | 0.01 | 0 - 0.02 (Beta) | |
| Adverse events - Rash - FTD/TPI + bevacizumab | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Thrombocytopenia - FTD/TPI + bevacizumab | 0.03 | 0.01 - 0.05 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Abdominal pain - FTD/TPI | 0.02 | 0 - 0.04 (Beta) | |
| Adverse events - Alanine aminotransferase increased - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Anaemia - FTD/TPI | 0.11 | 0.07 - 0.15 (Beta) | |
| Adverse events - Anorexia - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Aspartate aminotransferase increased - FTD/TPI | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Asthenia - FTD/TPI | 0.04 | 0.02 - 0.07 (Beta) | |
| Adverse events - Diarrhoea - FTD/TPI | 0.02 | 0.01 - 0.05 (Beta) | |
| Adverse events - Fatigue - FTD/TPI | 0.04 | 0.02 - 0.06 (Beta) | |
| Adverse events - Febrile neutropenia - FTD/TPI | 0.02 | 0.01 - 0.04 (Beta) | |
| Adverse events - Hand foot skin reaction - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hepatic failure - FTD/TPI | 0.02 | 0.01 - 0.05 (Beta) | |
| Adverse events - Hyperbilirubinaemia - FTD/TPI | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Hypertension - FTD/TPI | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Hypophosphataemia - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Intestinal obstruction - FTD/TPI | 0.02 | 0 - 0.04 (Beta) | |
| Adverse events - Jaundice - FTD/TPI | 0.02 | 0.01 - 0.04 (Beta) | |
| Adverse events - Leukopenia - FTD/TPI | 0.03 | 0.01 - 0.05 (Beta) | |
| Adverse events - Lipase increased - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Malignant neoplasm progression - FTD/TPI | 0.04 | 0.02 - 0.07 (Beta) | |
| Adverse events - Mucositis - FTD/TPI | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Neutropenia - FTD/TPI | 0.32 | 0.26 - 0.38 (Beta) | |
| Adverse events - Neutrophil count decreased - FTD/TPI | 0.05 | 0.03 - 0.08 (Beta) | |
| Adverse events - Pulmonary embolism - FTD/TPI | 0.02 | 0.01 - 0.04 (Beta) | |
| Adverse events - Rash - FTD/TPI | 0.00 | 0 - 0 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Thrombocytopenia - FTD/TPI | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Abdominal pain - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Alanine aminotransferase increased - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Anaemia - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Anorexia - BSC | 0.02 | 0.01 - 0.04 (Beta) | |
| Adverse events - Aspartate aminotransferase increased - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Asthenia - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Diarrhoea - BSC | 0.01 | 0 - 0.02 (Beta) | |
| Adverse events - Fatigue - BSC | 0.04 | 0.02 - 0.07 (Beta) | |
| Adverse events - Febrile neutropenia - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hand foot skin reaction - BSC | 0.00 | 0 - 0.01 (Beta) | |
| Adverse events - Hepatic failure - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hyperbilirubinaemia - BSC | 0.01 | 0 - 0.02 (Beta) | |
| Adverse events - Hypertension - BSC | 0.01 | 0 - 0.03 (Beta) | |
| Adverse events - Hypophosphataemia - BSC | 0.00 | 0 - 0.01 (Beta) | |
| Adverse events - Intestinal obstruction - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Jaundice - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Leukopenia - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Lipase increased - BSC | 0.01 | 0 - 0.02 (Beta) | |
| Adverse events - Malignant neoplasm progression - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Mucositis - BSC | 0.00 | 0 - 0.01 (Beta) | |
| Adverse events - Neutropenia - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Neutrophil count decreased - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Pulmonary embolism - BSC | 0.00 | 0 - 0 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Rash - BSC | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Thrombocytopenia - BSC | 0.00 | 0 - 0.01 (Beta) | |
| Adverse events - Abdominal pain - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Alanine aminotransferase increased - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Anaemia - Regorafenib | 0.02 | 0.01 - 0.03 (Beta) | |
| Adverse events - Anorexia - Regorafenib | 0.03 | 0.01 - 0.04 (Beta) | |
| Adverse events - Aspartate aminotransferase increased - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Asthenia - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Diarrhoea - Regorafenib | 0.06 | 0.04 - 0.08 (Beta) | |
| Adverse events - Fatigue - Regorafenib | 0.08 | 0.06 - 0.1 (Beta) | |
| Adverse events - Febrile neutropenia - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hand foot skin reaction - Regorafenib | 0.17 | 0.14 - 0.19 (Beta) | |
| Adverse events - Hepatic failure - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Hyperbilirubinaemia - Regorafenib | 0.03 | 0.02 - 0.04 (Beta) | |
| Adverse events - Hypertension - Regorafenib | 0.08 | 0.06 - 0.1 (Beta) | |
| Adverse events - Hypophosphataemia - Regorafenib | 0.04 | 0.03 - 0.06 (Beta) | |
| Adverse events - Intestinal obstruction - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Jaundice - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Leukopenia - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Lipase increased - Regorafenib | 0.04 | 0.02 - 0.05 (Beta) | |
| Adverse events - Malignant neoplasm progression - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Mucositis - Regorafenib | 0.02 | 0.01 - 0.04 (Beta) | |
| Adverse events - Neutropenia - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Neutrophil count decreased - Regorafenib | 0.00 | 0 - 0 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Pulmonary embolism - Regorafenib | 0.00 | 0 - 0 (Beta) | |
| Adverse events - Rash - Regorafenib | 0.06 | 0.04 - 0.07 (Beta) | |
| Adverse events - Thrombocytopenia - Regorafenib | 0.03 | 0.02 - 0.04 (Beta) | |
| ***AE costs*** | | | |
| Adverse events - Abdominal pain - unit cost | 204.36 | 164.31 - 244.42 (Normal) | B.3.5.3 |
| Adverse events - Alanine aminotransferase increased - unit cost | 2214.32 | 1780.32 - 2648.32 (Normal) | |
| Adverse events - Anaemia - unit cost | 703.48 | 565.6 - 841.36 (Normal) | |
| Adverse events - Anorexia - unit cost | 152.96 | 122.98 - 182.94 (Normal) | |
| Adverse events - Aspartate aminotransferase increased - unit cost | 2214.32 | 1780.32 - 2648.32 (Normal) | |
| Adverse events - Asthenia - unit cost | 703.48 | 565.6 - 841.36 (Normal) | |
| Adverse events - Diarrhoea - unit cost | 1746.82 | 1404.45 - 2089.19 (Normal) | |
| Adverse events - Fatigue - unit cost | 703.48 | 565.6 - 841.36 (Normal) | |
| Adverse events - Febrile neutropenia - unit cost | 3676.55 | 2955.96 - 4397.14 (Normal) | |
| Adverse events - Hand foot skin reaction - unit cost | 1581.81 | 1271.78 - 1891.83 (Normal) | |
| Adverse events - Hepatic failure - unit cost | 2262.30 | 1818.9 - 2705.7 (Normal) | |
| Adverse events - Hyperbilirubinaemia - unit cost | 152.96 | 122.98 - 182.94 (Normal) | |
| Adverse events - Hypertension - unit cost | 770.10 | 619.16 - 921.03 (Normal) | |
| Adverse events - Hypophosphataemia - unit cost | 152.96 | 122.98 - 182.94 (Normal) | |
| Adverse events - Intestinal obstruction - unit cost | 169.77 | 136.5 - 203.05 (Normal) | |
| Adverse events - Jaundice - unit cost | 703.48 | 565.6 - 841.36 (Normal) | |
| Adverse events - Leukopenia - unit cost | 627.97 | 504.89 - 751.05 (Normal) | |
| Adverse events - Lipase increased - unit cost | 205.78 | 165.45 - 246.11 (Normal) | |
| Adverse events - Malignant neoplasm progression - unit cost | 220.87 | 177.58 - 264.15 (Normal) | |
| Adverse events - Mucositis - unit cost | 152.96 | 122.98 - 182.94 (Normal) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse events - Neutropenia - unit cost | 627.97 | 504.89 - 751.05 (Normal) | |
| Adverse events - Neutrophil count decreased - unit cost | 627.97 | 504.89 - 751.05 (Normal) | |
| Adverse events - Pulmonary embolism - unit cost | 1905.92 | 1532.37 - 2279.47 (Normal) | |
| Adverse events - Rash - unit cost | 1581.81 | 1271.78 - 1891.83 (Normal) | |
| Adverse events - Thrombocytopenia - unit cost | 627.97 | 504.89 - 751.05 (Normal) | |
| ***Terminal care costs*** | | | |
| Terminal care cost | 7748.03 | 6229.44 - 9266.62 (Normal) | B.3.5.4 |
| ***AE disutilities*** | | | |
| Adverse event - Abdominal pain - disutility | -0.05 | -0.04 - -0.06 (Beta) | B.3.4.4 |
| Adverse event - Alanine aminotransferase increased - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Anaemia - disutility | -0.02 | -0.02 - -0.03 (Beta) | |
| Adverse event - Anorexia - disutility | -0.05 | -0.04 - -0.06 (Beta) | |
| Adverse event - Aspartate aminotransferase increased - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Asthenia - disutility | -0.07 | -0.06 - -0.09 (Beta) | |
| Adverse event - Diarrhoea - disutility | -0.05 | -0.04 - -0.06 (Beta) | |
| Adverse event - Fatigue - disutility | -0.07 | -0.06 - -0.09 (Beta) | |
| Adverse event - Febrile neutropenia - disutility | -0.15 | -0.12 - -0.18 (Beta) | |
| Adverse event - Hand foot skin reaction - disutility | -0.12 | -0.09 - -0.14 (Beta) | |
| Adverse event - Hepatic failure - disutility | -0.06 | -0.05 - -0.07 (Beta) | |
| Adverse event - Hyperbilirubinaemia - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Hypertension - disutility | -0.03 | -0.02 - -0.03 (Beta) | |
| Adverse event - Hypophosphataemia - disutility | -0.04 | -0.03 - -0.04 (Beta) | |
| Adverse event - Intestinal obstruction - disutility | -0.02 | -0.02 - -0.02 (Beta) | |
| Adverse event - Jaundice - disutility | -0.07 | -0.06 - -0.09 (Beta) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse event - Leukopenia - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Lipase increased - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Malignant neoplasm progression - disutility | -0.07 | -0.06 - -0.08 (Beta) | |
| Adverse event - Mucositis - disutility | -0.03 | -0.03 - -0.04 (Beta) | |
| Adverse event - Neutropenia - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Neutrophil count decreased - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Pulmonary embolism - disutility | -0.19 | -0.15 - -0.22 (Beta) | |
| Adverse event - Rash - disutility | -0.03 | -0.03 - -0.04 (Beta) | |
| Adverse event - Thrombocytopenia - disutility | -0.09 | -0.07 - -0.11 (Beta) | |
| Adverse event - Abdominal pain - duration | 15.60 | 12.54 - 18.66 (Normal) | |
| Adverse event - Alanine aminotransferase increased - duration | 26.67 | 21.44 - 31.89 (Normal) | |
| Adverse event - Anaemia - duration | 118.80 | 95.52 - 142.08 (Normal) | |
| Adverse event - Anorexia - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Aspartate aminotransferase increased - duration | 14.00 | 11.26 - 16.74 (Normal) | |
| Adverse event - Asthenia - duration | 27.60 | 22.19 - 33.01 (Normal) | |
| Adverse event - Diarrhoea - duration | 31.86 | 25.61 - 38.1 (Normal) | |
| Adverse event - Fatigue - duration | 6.25 | 5.03 - 7.47 (Normal) | |
| Adverse event - Febrile neutropenia - duration | 16.17 | 13 - 19.34 (Normal) | |
| Adverse event - Hand foot skin reaction - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Hepatic failure - duration | 7.33 | 5.9 - 8.77 (Normal) | |
| Adverse event - Hyperbilirubinaemia - duration | 39.00 | 31.36 - 46.64 (Normal) | |
| Adverse event - Hypertension - duration | 21.13 | 16.98 - 25.27 (Normal) | |
| Adverse event - Hypophosphataemia - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Intestinal obstruction - duration | 9.18 | 7.38 - 10.98 (Normal) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Adverse event - Jaundice - duration | 16.50 | 13.27 - 19.73 (Normal) | |
| Adverse event - Leukopenia - duration | 20.81 | 16.73 - 24.89 (Normal) | |
| Adverse event - Lipase increased - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Malignant neoplasm progression - duration | 9.88 | 7.94 - 11.81 (Normal) | |
| Adverse event - Mucositis - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Neutropenia - duration | 11.76 | 9.45 - 14.06 (Normal) | |
| Adverse event - Neutrophil count decreased - duration | 14.61 | 11.75 - 17.47 (Normal) | |
| Adverse event - Pulmonary embolism - duration | 70.67 | 56.82 - 84.52 (Normal) | |
| Adverse event - Rash - duration | 11.75 | 9.45 - 14.05 (Normal) | |
| Adverse event - Thrombocytopenia - duration | 34.63 | 27.84 - 41.41 (Normal) | |
| ***General population disutilities*** | | | |
| Male | 0.021213 | Multinormal (using variance/covariance matrix) | B.3.4.5 |
| Age | -0.000259 | | |
| Age² | -0.000033 | | |
| Constant | 0.950857 | | |
| ***Subsequent treatment*** | | | |
| Subsequent Trt - Regorafenib % | 0.30 | 0.44 - 0.23 (Dirichlet) | B.3.5.4 |
| Subsequent Trt - Capecitabine % | 0.07 | 0.07 - 0.07 (Dirichlet) | |
| Subsequent Trt - Doublet Chemotherapy % | 0.18 | 0.22 - 0.14 (Dirichlet) | |
| Subsequent Trt - Triplet Chemotherapy % | 0.04 | 0.03 - 0.05 (Dirichlet) | |
| Subsequent Trt - Fruquintinib % | 0.03 | 0.01 - 0.04 (Dirichlet) | |
| Subsequent Trt - FTD/TPI % | 0.02 | 0.01 - 0.03 (Dirichlet) | |
| Subsequent Trt - Irinotecan % | 0.02 | 0 - 0.03 (Dirichlet) | |
| Subsequent Trt - Nivolumab % | 0.01 | 0 - 0.03 (Dirichlet) | |

| Parameter | Value | CI (distribution) | Reference to Section in submission |
|---|---|---|---|
| Subsequent Trt - Bevacizumab+ doublet chemotherapy % | 0.09 | 0.09 - 0.09 (Dirichlet) | |
| Subsequent Trt - Bevacizumab + triplet chemotherapy % | 0.03 | 0.01 - 0.04 (Dirichlet) | |
| Subsequent Trt - Cetuximab + doublet chemotherapy % | 0.02 | 0.01 - 0.03 (Dirichlet) | |
| Subsequent Trt - Cetuximab+ triplet chemotherapy % | 0.01 | 0 - 0.02 (Dirichlet) | |
| Subsequent Trt - Ramucirumab + doublet chemotherapy % | 0.01 | 0 - 0.02 (Dirichlet) | |
| Subsequent Trt - Aflibercept + doublet chemotherapy % | 0.02 | 0 - 0.03 (Dirichlet) | |
| Subsequent Trt - Panitumumab + doublet chemotherapy % | 0.03 | 0.02 - 0.04 (Dirichlet) | |
| Subsequent Trt - Capecitabine + oxaliplatin % | 0.08 | 0.07 - 0.08 (Dirichlet) | |
| Subsequent Trt - Bevacizumab + capecitabine % | 0.03 | 0.01 - 0.04 (Dirichlet) | |
| Proportion receiving subsequent trt - FTD/TPI + bevacizumab | 0.58 | 0.47 - 0.7 (Beta) | B.3.5.4 |
| Proportion receiving subsequent trt - FTD/TPI | 0.58 | 0.47 - 0.7 (Beta) | |
| Proportion receiving subsequent trt - BSC | 0.00 | Fixed | |
| Proportion receiving subsequent trt - Regorafenib | 0.58 | 0.47 - 0.7 (Beta) | |

**Key:** AE, adverse event; BSA, body surface area; BSC, best supportive care; CI, confidence interval; CT, computerised tomography; FTD/TPI, trifluridine-tipiracil; GP, general practitioner; HR, hazard ratio; IV, intravenous; kg, kilogram; LY, life-year; mg, milligram; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dosing intensity; ToT; time on treatment; Trt, treatment;

### B.3.9.2Assumptions

A summary of key model assumptions are provided in Table 62.

**Table 62: Summary of key modelling assumptions**

| Topic | Assumption | Justification/reason |
|---|---|---|
| Cycle length | Model cycle length of 1 week is appropriate | A weekly cycle length is assumed to be sufficiently short enough to represent the frequency of clinical events and interventions and is aligned with the administration of the multiple treatments included within the model (treatment cycles in weeks). |
| Time horizon | A lifetime time horizon of 15 years is appropriate | The economic model runs for 15 years to reflect the maximum lifetime of patients based on a starting age of 62. The impact of varying time horizon on the results was tested in sensitivity analysis. |
| Comparators | ToT data for regorafenib was assumed to equal PFS | ToT from the active treatment comparators outside of the SUNLIGHT trial data (regorafenib) was limited therefore alternative approaches were considered.<br>It is expected that patients will stop treatment upon progression and SUNLIGHT data showed similar outcomes of PFS and ToT. |
| Efficacy | Individual models have been fit to each treatment arm where patient-level data was available | Log cumulative hazard plots showed some support for the proportional hazard assumption. However, given the availability of patient-level data for each treatment, the reliance on the proportional hazard assumption was deemed unnecessary for some treatments and therefore, independent models were deemed more appropriate. |
| | Identification of the most appropriate survival curves describing OS, PFS and ToT | Extensive analyses have been undertaken to identify appropriate survival curves describing the efficacy of each treatment, with reference to the guidance from the NICE DSU. However, to address the uncertainty around these parameters, scenario analyses have been conducted by applying alternative PSMs. |

| Topic | Assumption | Justification/reason |
|---|---|---|
| Treatment costs | BSC costs are assumed to be captured in routine visits | This is consistent with the assumptions used in previous NICE appraisals.[44,45] |
| | Administration costs of oral treatments are assumed to be captured in routine monitoring | Patients on oral treatments are assumed to attend an oral chemotherapy outpatient appointment (per 4 weeks). During this appointment they are assumed to receive treatment for the upcoming cycle, undergo routine tests and see a clinician to review their treatment as per previous NICE appraisals.[44,45] |
| Subsequent treatments | All treatments are assumed to have the same distribution as per the SUNLIGHT trial using the pooled data. | Given the uncertainty of what patients would receive after each 3L treatment. Alternative options are explored in scenario analysis. |

**Key:** 3L, third-line; BSC, best supportive care; DSU, decision support unit; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; ToT, time on treatment

### *B.3.10 Base case results*

Base case deterministic results are presented throughout this section. As advised by the NICE team at the decision problem meeting, deterministic results are presented using both the 1.2x and 1.7x severity modifiers. Throughout the results, the trifluridine-tipiracil PAS price is applied. Servier is aware that the list price of bevacizumab is likely to vary due to the availability of biosimilars on the market and loss of exclusivity, and this will impact the deterministic results (and cost-effectiveness) of trifluridine-tipiracil plus bevacizumab versus relevant comparators. Regorafenib is also likely to have a PAS. However, as the cost of both are unknown, the list price of bevacizumab and regorafenib has been used throughout this section (and as such will impact the interpretability of the results throughout).

Base case deterministic pairwise results are presented in Table 63 (with trifluridine-tipiracil PAS). Within this table both severity weightings are presented (x1.2 and x1.7). Table 64 and Table 65 present incremental results when applying the x1.2 and x1.7 severity modifiers respectively.

Table 66 presents the net-health benefit (NHB) at the £20,000/QALY and £30,000/QALY willingness-to-pay (WTP). Within this table all severity weightings are presented.

**Table 63: Base case results – pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7)**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.64 | 0.43 | [redacted] | 0.72 | 0.51 | 0.62 | 0.87 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.84 | 0.56 | [redacted] | 0.51 | 0.38 | 0.45 | 0.64 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 64: Base case results – incremental analysis (with PAS) – 1.2x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.43 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.23 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.06 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.39 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 65: Base case results – incremental analysis (with PAS) – 1.7x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.43 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.32 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.09 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.55 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 66: Pairwise NHB (with PAS) - all severity modifiers (no weight, x1.2 and x1.7)**

| Technologies: Trifluridine-tipiracil + bevacizumab versus: | Incremental QALYs | | | NHB at £20,000 | | | NHB at £30,000 | | |
|---|---|---|---|---|---|---|---|---|---|
| | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BSC | 0.51 | 0.62 | 0.87 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Regorafenib | 0.38 | 0.45 | 0.64 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; NHB, net-health benefit; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

## *B.3.11 Exploring uncertainty*

### B.3.11.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA. In PSA, all parameters are simultaneously varied from an assigned probability distribution (see Table 61). PSA inputs were randomly drawn, and results recorded across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty.

Pairwise and incremental probabilistic results are presented in Table 67 - Table 69, at the different 1.2x and 1.7x severity weightings. The probabilistic results show consistency with the deterministic results.

Figure 32 - Figure 37 present the cost-effectiveness plane (for trifluridine-tipiracil with bevacizumab versus trifluridine-tipiracil, regorafenib and BSC at the 1.2x and 1.7x severity weightings).

Figure 38 presents the cost-effectiveness acceptability curve (CEAC). As the CEAC is based on the net-monetary benefit of each treatment, no severity weighting is presented here.

**Table 67: PSA results – pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7)**

| Technologies | Total | | Incremental | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | QALY | Costs (£) | QALYs | | | | | |
| | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.44 | [redacted] | 0.51 | 0.61 | 0.86 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.60 | [redacted] | 0.34 | 0.41 | 0.59 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 68: PSA results – incremental analysis (with PAS) – 1.2x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.44 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.22 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.60 | [redacted] | -0.02 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.39 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 69: PSA results – incremental analysis (with PAS) – 1.7x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.44 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.31 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.60 | [redacted] | -0.03 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.55 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years



**Figure 32: Cost-effectiveness plane (versus trifluridine-tipiracil) - 1.2x severity weighting**

**Key:** QALYs, quality-adjusted life years

**Figure 33: Cost-effectiveness plane (versus trifluridine-tipiracil) - 1.7x severity weighting**

**Key:** QALYs, quality-adjusted life years



**Figure 34: Cost-effectiveness plane (versus regorafenib) -1.2x severity weighting**

**Key:** QALYs, quality-adjusted life years

**Figure 35: Cost-effectiveness plane (versus regorafenib) -1.7x severity weighting**

**Key:** QALYs, quality-adjusted life years



**Figure 36: Cost-effectiveness plane (versus BSC) - 1.2x severity weighting**

**Key:** BSC, best supportive care; QALYs, quality-adjusted life years

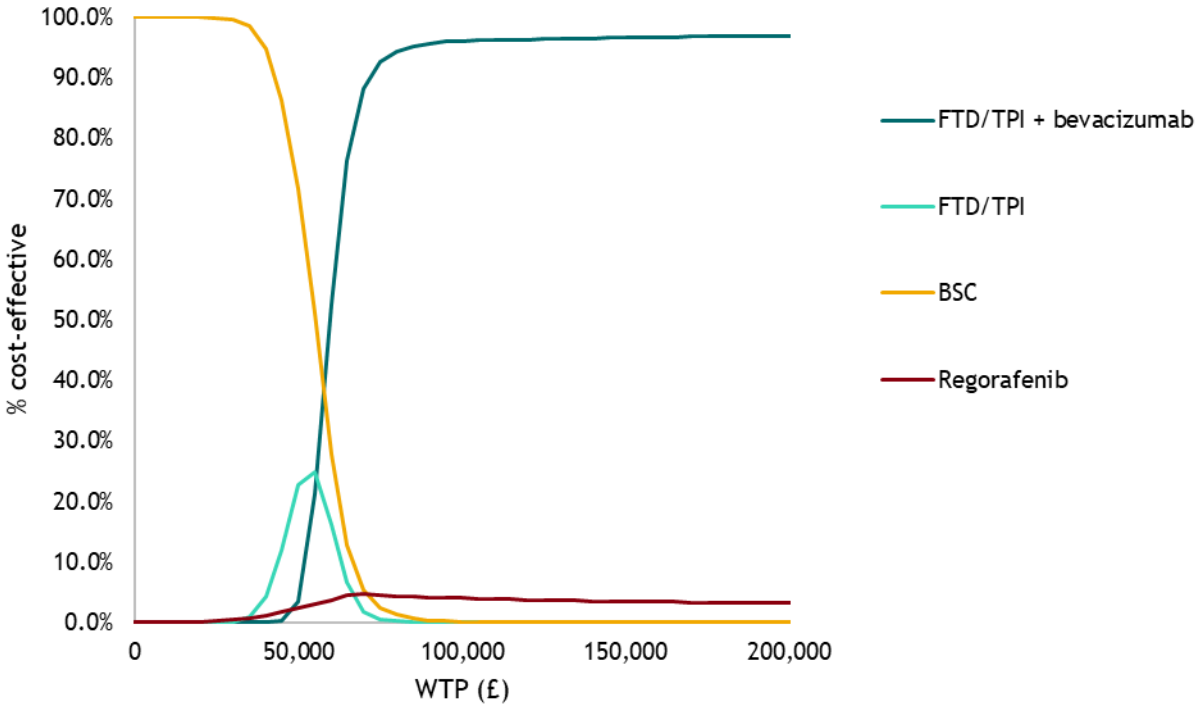
**Figure 37: Cost-effectiveness plane (versus BSC) - 1.7x severity weighting**

**Key:** BSC, best supportive care; QALYs, quality-adjusted life years



**Figure 38: Cost-effectiveness acceptability curve (with no severity weighting)**




**Key:** BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; WTP, willingness-to-pay

### B.3.11.2 Deterministic sensitivity analysis

OWSA was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, while keeping all else as per the base case. In turn, inputs were set to their respective lower and upper limits (presented in Table 61). If the variance of a parameter was not available, a simplifying assumption was made assuming that the standard error was 10% of the mean value. Correlated inputs with joint uncertainty, such as parametric survival model coefficients and utility regression model coefficients, which are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

Figure 39 - Figure 44 present the tornado plots showing the ten parameters which had the largest impact on the incremental net-monetary benefit (INMB) for trifluridine-tipiracil with bevacizumab versus trifluridine-tipiracil, regorafenib and BSC at the x1.2 and x1.7 severity weightings. The parameters which had the largest impact on results were RDI's for active treatments and HRs for the non-trial comparators.

**Figure 39: Tornado plot of OWSA (iNMB, versus trifluridine-tipiracil) – 1.2x severity weighting**

**Key:** FTD/TPI, trifluridine-tipiracil; iNMB, incremental net-monetary benefit; IV, intravenous; RDI, relative dose intensity

**Figure 40: Tornado plot of OWSA (iNMB, versus trifluridine-tipiracil) – 1.7x severity weighting**

**Key:** FTD/TPI, trifluridine-tipiracil; iNMB, incremental net-monetary benefit; IV, intravenous; RDI, relative dose intensity



**Figure 41: Tornado plot of OWSA (iNMB, versus regorafenib) – 1.2x severity weighting**

**Key:** FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity

**Figure 42: Tornado plot of OWSA (iNMB, versus regorafenib) – 1.7x severity weighting**

**Key:** FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity



**Figure 43: Tornado plot of OWSA (iNMB, versus BSC) – 1.2x severity weighting**

**Key:** BSC, best supportive care; CT, computerised tomography; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity

**Figure 44: Tornado plot of OWSA (iNMB, versus BSC) – 1.7x severity weighting**

**Key:** BSC, best supportive care; CT, computerised tomography; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity



#### B.3.11.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. To fully interpret uncertainty, several scenarios were considered related to:

- Time horizon and discount rates
- Drug wastage assumptions
- Dosing assumptions
- Subsequent treatment
- HRQL
- Efficacy assumptions related to OS, PFS and ToT

As the base case probabilistic results and deterministic results were very similar, all scenario analyses were conducted deterministically. Results of the scenario analysis (across both the 1.2x and 1.7x severity weighting) are presented in Table 70.

Results appear robust to changes in modelling assumptions, with the most sensitivity to the ICER associated with the OS parametric curve selection.

**Table 70: Deterministic scenario analysis**

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | ICER versus regorafenib | | ICER versus BSC | |
|---|---|---|---|---|---|---|---|---|
| | | | x1.2 | x1.7 | x1.2 | x1.7 | x1.2 | x1.7 |
| Time horizon | 15 years | 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 20 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Discount rates | 3.5% | 0.0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 6.0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug wastage | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RDI | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RDI source for regorafenib | Same as trifluridine/tipiracil | CORRECT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Source for subsequent treatments | SUNLIGHT pooled | No subsequent treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | SUNLIGHT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | UK practice (20% trifluridine-tipiracil+bev; 50% others) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | UK practice (40% all) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Age-adjusted disutility | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Utility option | SUNLIGHT - treatment independent | SUNLIGHT - pooled treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | TA866 - Regorafenib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | ICER versus regorafenib | | ICER versus BSC | |
|---|---|---|---|---|---|---|---|---|
| | | | x1.2 | x1.7 | x1.2 | x1.7 | x1.2 | x1.7 |
| | | TA405 - FTD/TPI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| AE disutility | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS distribution | Log-logistic | 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] |
| PFS distribution | Log-normal | 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] |
| ToT distribution (trifluridine-tipiracil + bevacizumab (trifluridine-tipiracil) | Weibull | 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] |
| ToT distribution (trifluridine-tipiracil + | Weibull | Exponential | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Generalised Gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |



| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | ICER versus regorafenib | | ICER versus BSC | |
|---|---|---|---|---|---|---|---|---|
| | | | x1.2 | x1.7 | x1.2 | x1.7 | x1.2 | x1.7 |
| bevacizumab (bevacizumab) | | 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] |
| ToT distribution (trifluridine-tipiracil) | Generalised Gamma | 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] |
| NMA option | Random-effects | Fixed-effects | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Regorafenib ToT | Assume same as PFS | Use PFS NMA HR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** AE, adverse event; BSA, body surface area; BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; ToT, time on treatment



### *B.3.12 Subgroup analysis*

A subgroup analysis was conducted based on prior bevacizumab use using only patients from the SUNLIGHT study who had not received prior bevacizumab which is more aligned to current UK practice. Specific inputs for the subgroup analysis are presented in Appendix M.

As described in Section B.2.7 this subgroup is presented for completeness. However, prior bevacizumab use is not considered a treatment effect modifier and clinical opinion received as part of this submission considers the ITT SUNLIGHT population to be generalisable to the UK.[4]

The deterministic pairwise results for the no prior bevacizumab subgroup are presented in Table 71 (with trifluridine-tipiracil PAS). Within this table both severity weightings are presented (x1.2 and x1.7). Table 72 and Table 73 present incremental results when applying the x1.2 and x1.7 severity modifiers respectively.

**Table 71: Subgroup results – pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – no prior bevacizumab**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.95 | 1.33 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 1.00 | 0.71 | 0.85 | 1.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.90 | 0.60 | [redacted] | 1.05 | 0.73 | 0.88 | 1.24 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 1.22 | 0.81 | [redacted] | 0.73 | 0.52 | 0.63 | 0.89 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 72: Subgroup results – incremental analysis (with PAS) – 1.2x severity weighting – no prior bevacizumab**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.60 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.03 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.81 | [redacted] | 0.22 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.33 | [redacted] | 0.63 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 73: Subgroup results – incremental analysis (with PAS) – 1.7x severity weighting – no prior bevacizumab**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.60 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.04 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.81 | [redacted] | 0.31 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.33 | [redacted] | 0.89 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

## *B.3.13 Benefits not captured in the QALY calculation*

Although the QALY calculation estimated as part of this submission captures the majority of benefits directly related to the patient such as delayed progression and improved quality of life, there is no consideration of the indirect benefits that the combination of trifluridine-tipiracil plus bevacizumab may offer for carers supporting those with mCRC.

## *B.3.14 Validation*

### B.3.14.1 Independent technical cost-effectiveness model quality-check (QC)

The cost-effectiveness model was quality assured by an experienced health economist who was not involved in the development of the model. As part of this QC process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs and outputs. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g., how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g., if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g., is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

### B.3.14.2 Expert validation of cost-effectiveness analysis

Key model assumptions were also validated by UK clinical experts including:

- Treatment discontinuation
- Plausibility of parametric survival models
- Health care resource estimates
- Subsequent therapies

Details of the clinical validation can be found in Appendix Q Internal validation

OS, PFS and ToT Kaplan-Meier data from the SUNLIGHT trial were compared with the PFS, OS and ToT outputs from the model (see Appendix J).

For both trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil, the model survival projections appear in line with the observed trial data for all outcomes; OS, PFS and ToT.

#### B.3.14.3 Validation against published literature

Validation of the comparator arms was conducted using published clinical studies available in the mCRC setting for each treatment which was considered feasible to include within the NMA (see Section B.2.9).

##### *B.3.14.3.1 Trifluridine-tipiracil*

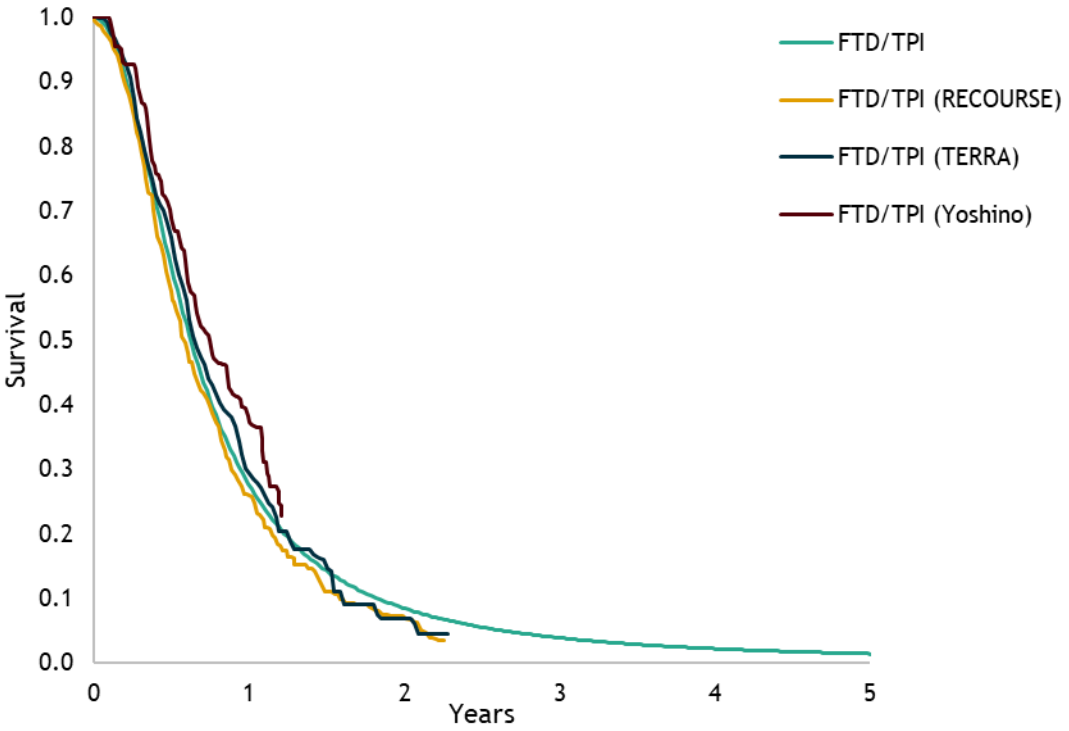
The following sources were used to externally validate the modelled trifluridine-tipiracil outcomes:

- RECOURSE[52] is a phase III randomised control trial comparing trifluridine-tipiracil monotherapy with BSC versus placebo with BSC for patients with adenocarcinoma of the colon or rectum who had received two or more previous treatments.
- TERRA[53] is a phase III randomised control trial of trifluridine-tipiracil monotherapy in Asian patients with previously treated mCRC versus placebo.
- Yoshino et al, 2012[54] is a Phase II placebo-controlled trial of Japan patients who had confirmed mCRC and a treatment history of two or more regimens.

The modelled outcomes for both OS and PFS are consistent with the published studies for trifluridine-tipiracil with all of the KM data following a similar shape and being visually close (Figure 45 and Figure 46).

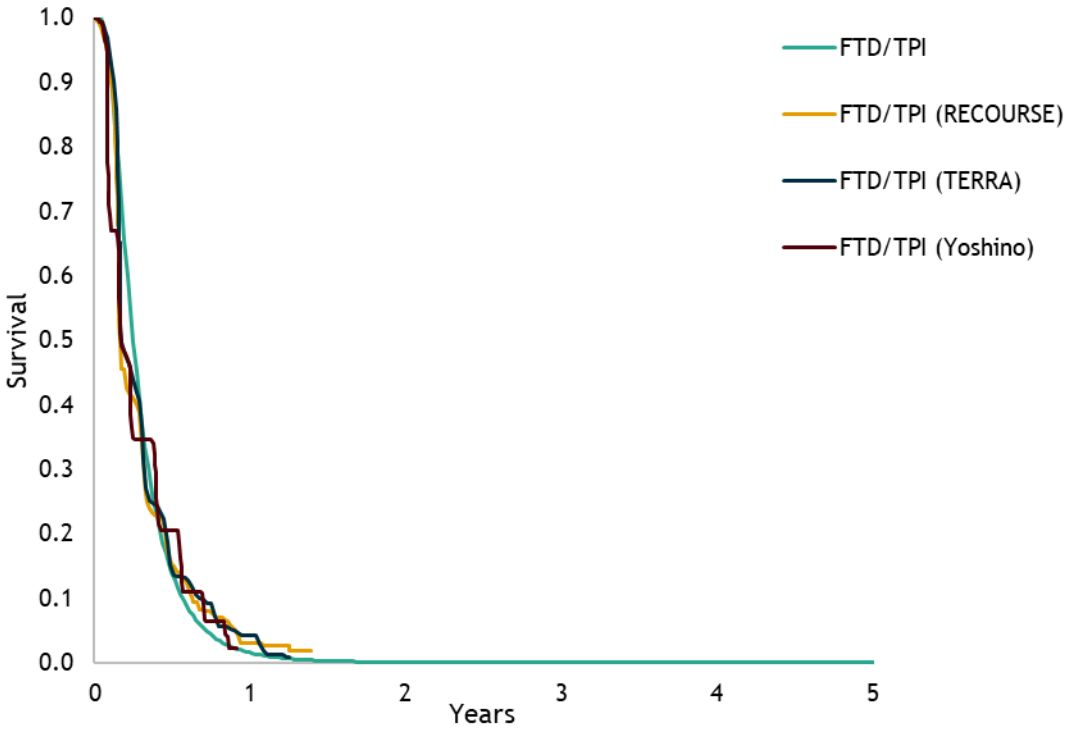

 

**Figure 45: External validation – trifluridine-tipiracil – OS**




**Key:** FTD/TPI, trifluridine-tipiracil; OS, overall survival

**Figure 46: External validation – trifluridine-tipiracil – PFS**




**Key:** FTD/TPI, trifluridine-tipiracil; PFS, progression-free survival

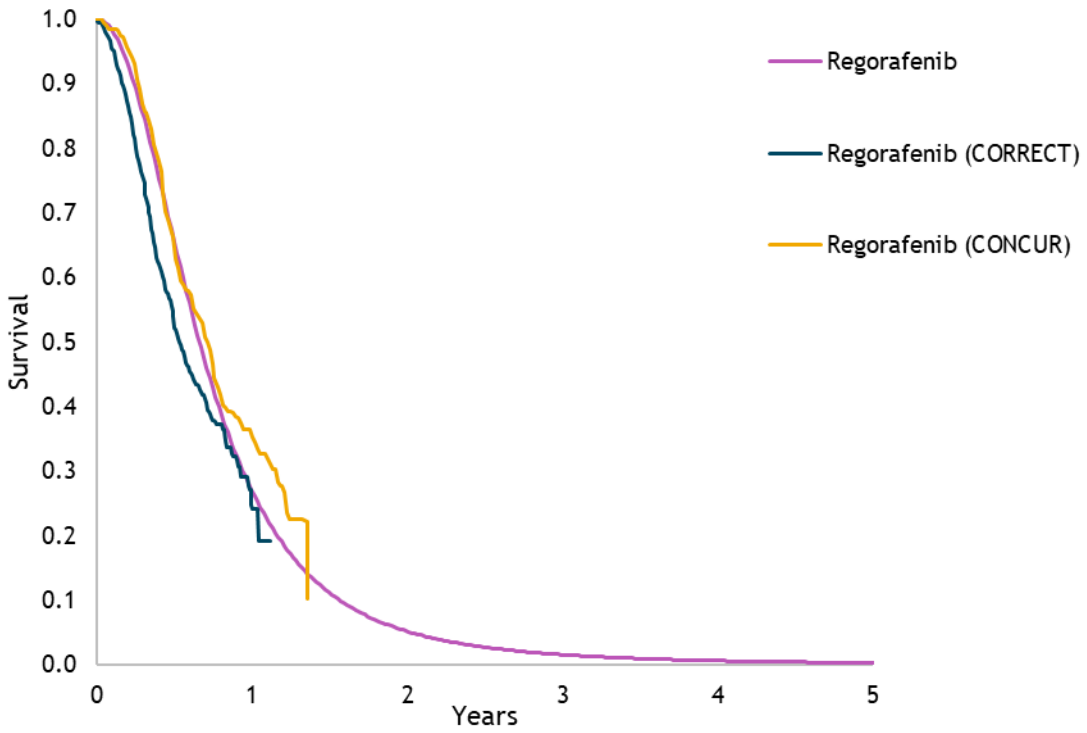
#### *B.3.14.3.2 Regorafenib*

The following sources were used to externally validate the modelled regorafenib outcomes:

- CONCUR[49] is a placebo-controlled randomised control Phase III trial of regorafenib with best supportive care versus placebo and best supportive care in Asian patients with previously treated mCRC.
- CORRECT[50] is a Phase III randomised control trial of regorafenib versus placebo for previously treated mCRC patients.

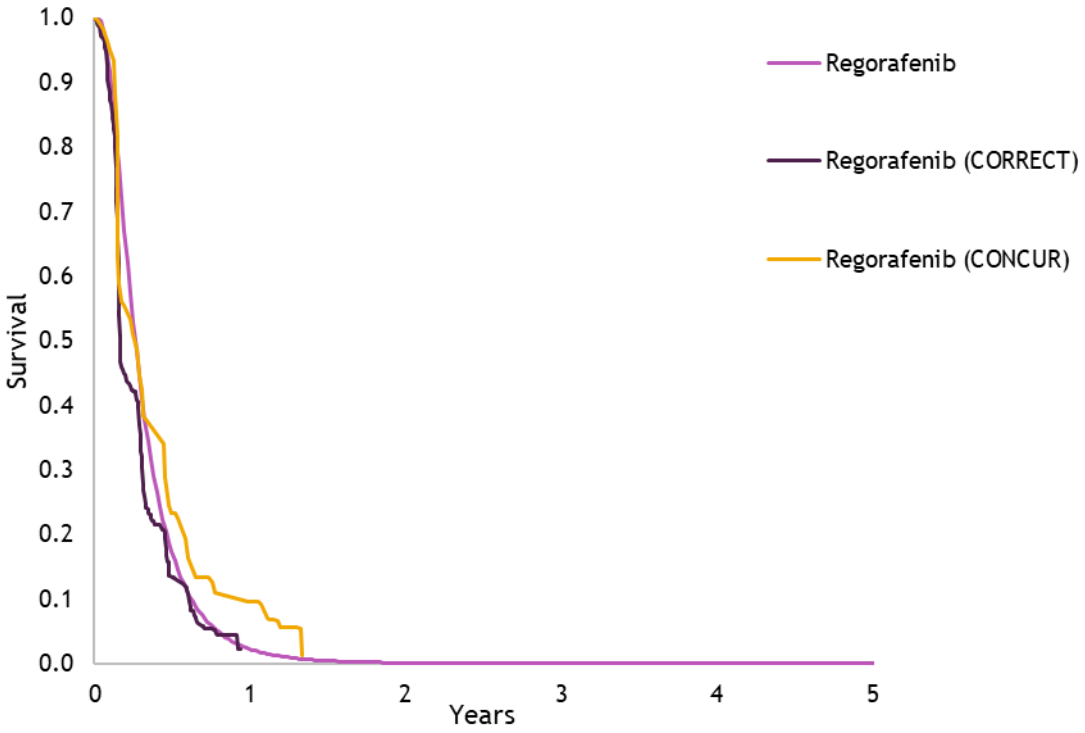
The modelled OS and PFS outcomes for regorafenib looks consistent with the published outcomes (Figure 47 and Figure 48)

**Figure 47: External validation – Regorafenib – OS**




**Key:** OS, overall survival

**Figure 48: External validation – Regorafenib – PFS**




**Key:** PFS, progression-free survival

#### *B.3.14.3.3 BSC*

There are a multitude of sources available to use as cross-validation for the BSC arm of the economic model. This is primarily due to BSC being the control arm in the majority of trials if using placebo is considered as a proxy. A comparison is of the modelled BSC OS and PFS versus the available literature are presented in Figure 49 and Figure 50. The following sources were used to externally validate the modelled BSC outcomes:

- RECOURSE[52] is a phase III randomised control trial comparing FTD/TPI monotherapy with BSC versus placebo with BSC for patients with adenocarcinoma of the colon or rectum who had received two or more previous treatments.
- TERRA[53] is a phase III randomised control trial of FTD/TPI monotherapy in Asian patients with previously treated mCRC versus placebo.
- Yoshino et al, 2012[54] 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[91] is a Phase III open-label trial comparing panitumumab with BSC with BSC alone in previously treated mCRC patients.

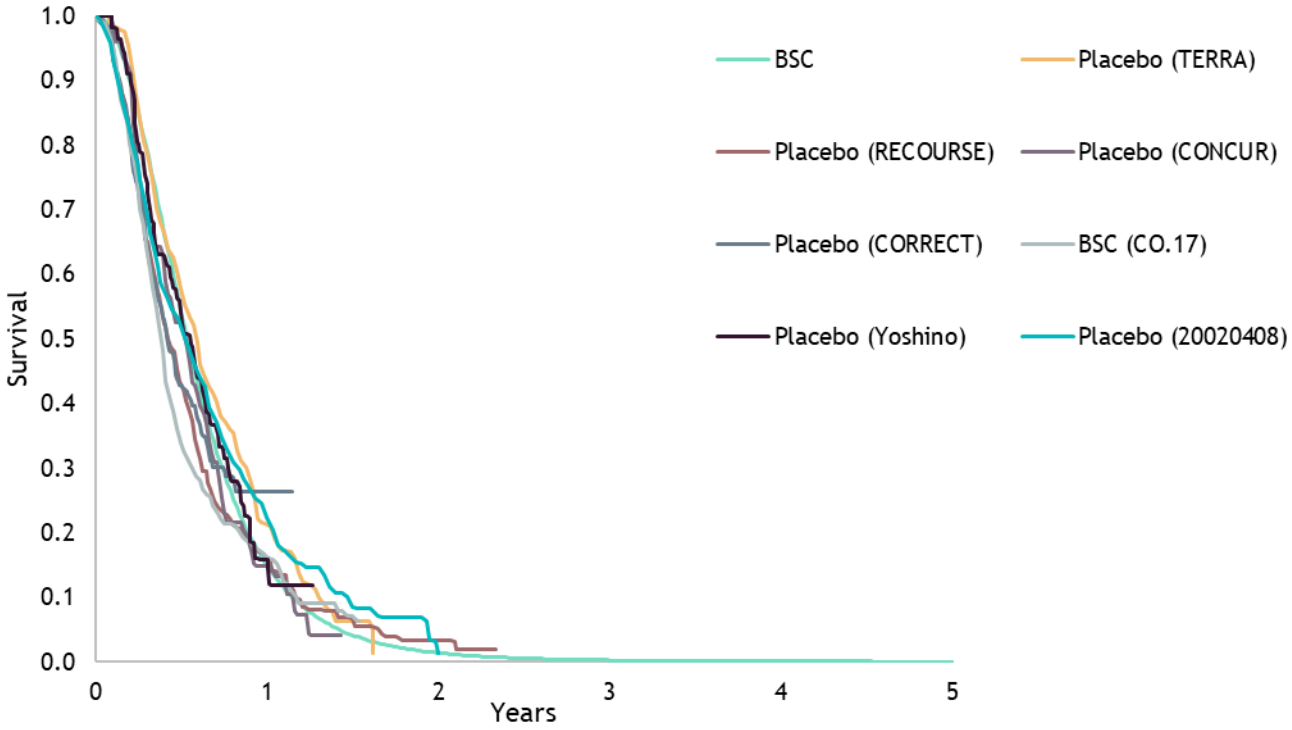

 

- CO.17[92] is a study comparing cetuximab to BSC in patients with advanced CRC expressing EGFR previously treated with fluoropyrimidine, oxaliplatin and irinotecan with no response.
- CONCUR[49] is a placebo-controlled randomised control Phase III trial of regorafenib with best supportive care versus placebo and best supportive care in Asian patients with previously treated mCRC.
- CORRECT[50] is a Phase III randomised 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 49). 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.

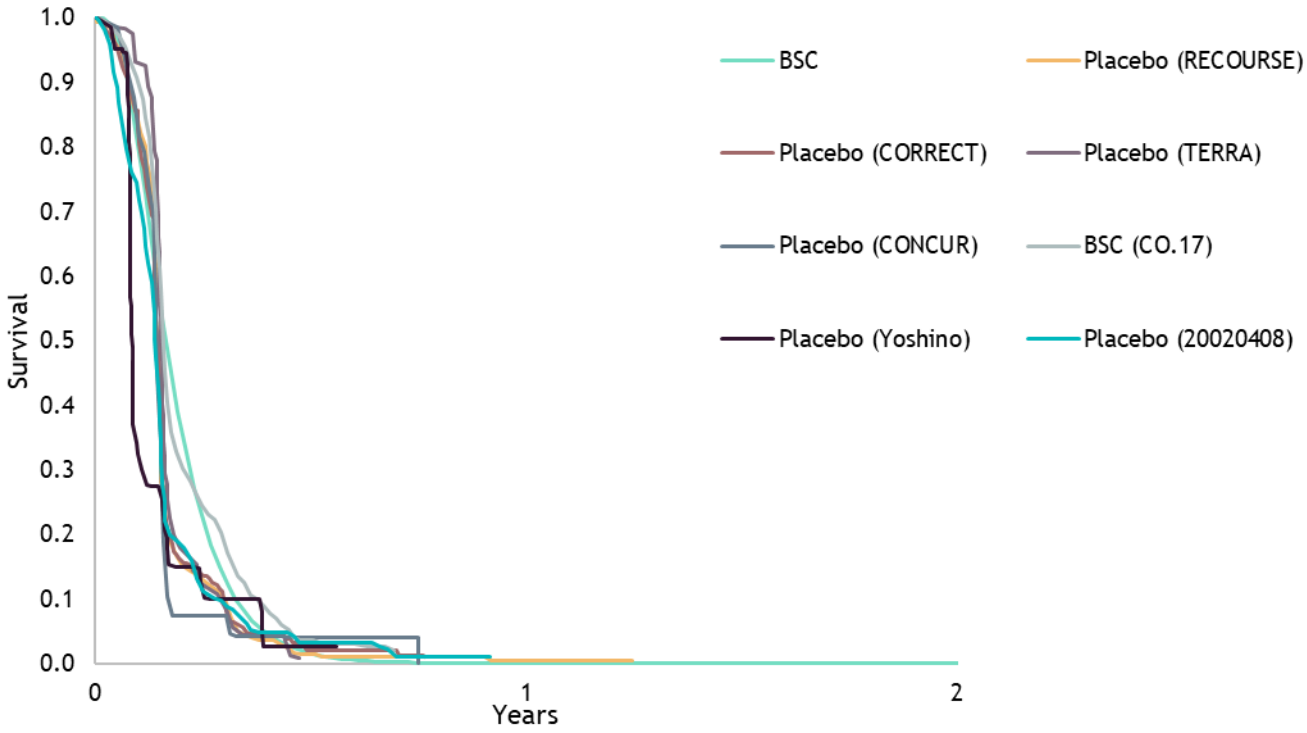
For PFS, the modelled BSC outcomes look consistent with the CO.17 outcomes but may slightly overestimate outcomes compared to the other sources between 3 to 6 months (Figure 50). However, as with OS, the 'longer-term' estimates are all consistent with all sources projecting little or no patients' progression-free by 1 year.

**Figure 49: External validation – BSC – OS**




**Key:** BSC, Best supportive care; OS, overall survival

**Figure 50: External validation – BSC – PFS**




**Key:** BSC, best supportive care; PFS, progression-free survival

### *B.3.15 Interpretation and conclusions of economic evidence*

The economic analysis performed uses a simplified model, designed to represent the mCRC pathway while capturing relevant health outcomes. The model structure is consistent with previous mCRC economic evaluations and combines the most relevant efficacy and safety clinical data, using robust statistical techniques to establish the comparative efficacy of trifluridine-tipiracil plus bevacizumab versus standard of care in patients with mCRC at third-line.

The availability of patient-level data from the SUNLIGHT provides a direct comparison with trifluridine monotherapy which is one of the treatments recommended at third-line and used in UK clinical practice. The main limitation of the economic analysis presented is the lack of direct comparative efficacy with the other relevant comparators within the third-line setting (regorafenib and BSC). Despite this limitation, analysis has been conducted utilising the most appropriate available data for each comparator, with all appropriate statistical adjustments being made in order to perform an unbiased comparison within a network meta-analysis framework.

A further potential limitation of the analysis is the reliance on information sourced within the literature. In some instances, the studies used to inform the NMA reflect different populations in different treatment lines instead of majority third-line population as per SUNLIGHT (e.g,. the RECOURSE trial which is at a 2L setting). Despite this, the impact of this is expected to be small as, statistical analyses using data from the RECOURSE trial shows no evidence to suggest that treatment line is a treatment effect modifier. As such, the network meta-analysis informing the relative efficacy estimates for non-direct comparators (regorafenib and BSC) is considered relevant to estimate the efficacy compared to trifluridine plus bevacizumab.

Model extrapolations were chosen based on the most appropriate statistical and visual fit taking into account clinical plausibility. Survival rates for patients diagnosed with mCRC who have received two prior lines of therapy are poor and can have a significant impact on quality of life. There are limited effective treatments available, therefore treatments which offer extension of life without impairing quality of life are important for this disease area.

The interpretation of results is limited without the knowledge of treatment discounts for regorafenib and bevacizumab. However, based on the results including the 1.2x and 1.7x severity modifier, Servier believe that the estimates should lie within an acceptable willingness-to-pay threshold.

Overall, results from the economic analysis infer that trifluridine-tipiracil with bevacizumab represents both a clinically and potentially cost-effective treatment option for patients with mCRC who have had two prior lines of therapy.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

## Summary of Information for Patients (SIP)

**December 2023**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]_SIP | 1.0 | no | December 2023 |

# Summary of Information for Patients (SIP):

## The pharmaceutical company perspective

### What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

### SECTION 1: Submission summary

**1a) Name of the medicine** (generic and brand name):

| |
|---|
| Trifluridine tipiracil (Lonsurf) with bevacizumab |

**1b) Population this treatment will be used by.** Please outline the main patient population that is being appraised by NICE:

| |
|---|
| Adults with metastatic colorectal cancer after 2 systemic treatments |

**1c) Authorisation:** Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

| |
|---|
| Actual CHMP Opinion date 22/06/2023<br>Actual EC decision date 26/07/2023<br>UK regulatory approval 2/11/2023 |

**1d) Disclosures.** Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

| |
|---|
| Lynch Syndrome (UK) ; £3,564 ; To further raise awareness to the general population for a condition that was once regarded as a rare genetic disorder by distributing pin/badge amongst our patient support network and the learning candidates especially during the annual lynch awareness day. |

Fortuneswell Cancer Trust / Charity ; £4500 ; grant to support a chemotherapy outreach service

Bowel Cancer UK; £945 presentation at company meeting from Genevieve Edwards who is the CEO of BCUK

## SECTION 2: Current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Colorectal cancer (CRC) involves the large intestine and the rectum, the lowest part of the digestive system. Colon cancer accounts for 72% of CRCs and rectal cancer for 28% of CRCs

CRC is the fourth most common cancer in the UK; there were 34,825 new cases in England in 2017, which accounted for 11% of all new cancer cases. The current incidence of CRC in England is 68 incidence cases per 100,000

Around 4 in 10 (43%) new cases of colorectal cancer in the UK were in people aged over 75 years, but it can affect young people too.

Stage IV metastatic CRC (mCRC) is an advanced form of CRC that has spread beyond the large intestine and nearby lymph nodes, typically spreading first to the liver.[1] Patients with Stage IV mCRC have a poor prognosis, with 1-year survival rates of approximately 44%, and 5-year survival rates of less than 10%.. Survival outcomes in the ≥ 3L setting are particularly poor, ranging between 6–12 months.

Most patients with mCRC present with disease that cannot be cured by surgery. For these patients, the objective of treatment is to control disease progression and prolong life, while maintaining quality of life.

### 2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

CRC can be discovered at any stage, from asymptomatic cancer identified by screening through to presentation as a surgical emergency

Currently, the most common route to diagnosis is through a visit to the GP with non-urgent symptoms, although approximatively 25% of cases present as an emergency

The simplest method of diagnosis is via rectum examination.

Physical examination, blood counts, and renal and liver function tests are used to determine if the CRC has progressed to metastatic disease ie spread, and is then confirmed by radiological imaging, usually a CT, MRI, or ultrasound scan.

**2c) Current treatment options:**

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Figure 1 illustrates the treatment pathway for mCRC in England, based on guidance issued by the National Institute for Health and Care Excellence (NICE) across all technology appraisals. It also highlights where the combination of trifluridine tipiracil and bevacizumab would potentially fit. In the NHS in England, treatment decisions for mCRC are based on genetic testing (biomarker driven) and treatment in later-lines is informed by prior therapy. First and second-line treatment of mCRC is dominated by chemotherapy combination regimens, which are typically FOLFOX or XELOX (oxaliplatin and capecitabine), and less commonly FOLFOXIRI (oxaliplatin, leucovorin, 5-FU, and irinotecan) which accounts for only 10% of all front-line treatments for mCRC). For patients with specific mutations, clinicians have the additional choice of including biologics in the first-line setting .

Figure 1

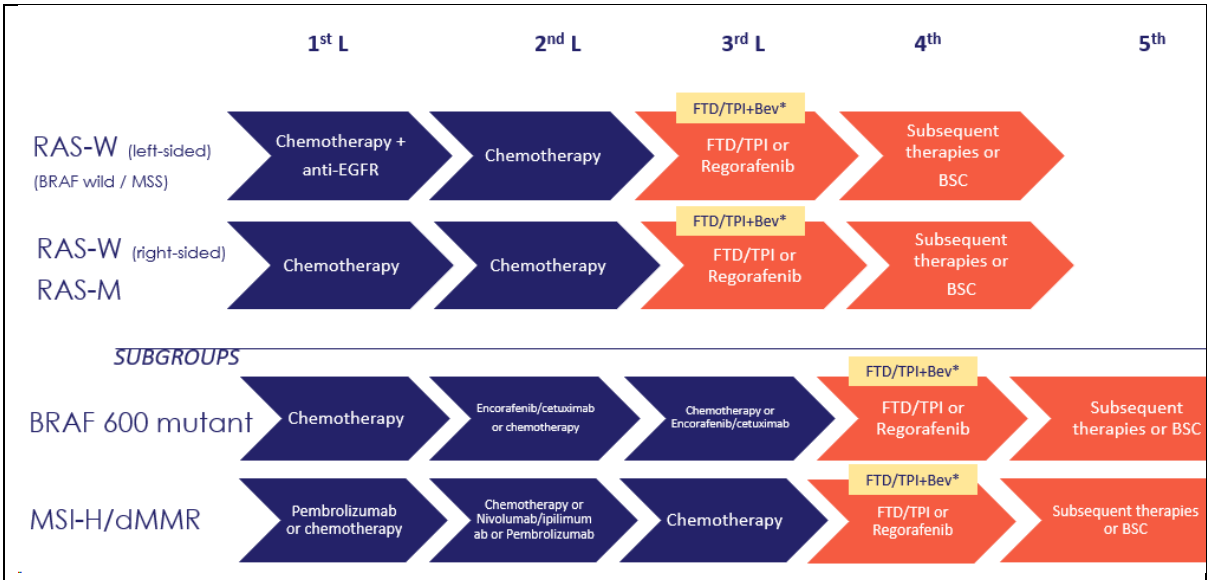



**Figure adapted from NICE guidance and feedback of mCRC Therapy Area Experts**
Chemotherapy can be FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5FU, oxaliplatine/ irinotecan). BSC, Best Supportive Care. FTD/TPI+Bev, Trifluridine/tipiracil + bevacizumab

### 2d) Patient-based evidence (PBE) about living with the condition

**Context:**

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Prometco study-The purpose of PROMETCO is to provide real-world data on overall survival, treatment patterns, associated effectiveness and safety, and impact on patients with mCRC throughout the continuum of care Prometco - HOME
18 countries, 98 investigational sites with 738 patients enrolled. 77 Uk patients enrolled
https://www.futuremedicine.com/doi/10.2217/fon-2022-1253

## SECTION 3: The treatment

**3a) How does the new treatment work?**

| What are the important features of this treatment?<br><br>Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body<br><br>Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.<br>If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these. |
|---|
| Trifluridine tipiracil is a type of cancer chemotherapy which belongs to the group of medicines called cytostatic antimetabolite medicines. It contains two different active substances: trifluridine and tipiracil. Trifluridine stops the growth of cancer cells. Tipiracil stops the trifluridine from being broken down by the body, helping trifluridine to work longer.<br>Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour. |

**3b) Combinations with other medicines**

| Is the medicine intended to be used in combination with any other medicines?<br>• Yes / No<br>If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.<br><br>If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.<br><br>**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.** |
|---|
| As above |

**3c) Administration and dosing**

| How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.<br><br>How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments? |
|---|

Lonsurf is an oral tablet 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)

When Lonsurf is used in combination with bevacizumab for the treatment of CRC, the recommended dose of Lonsurf is 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle for as long as benefit is observed or until unacceptable toxicity occurs

Bevacizumab is administered by intravenous infusion and supplied in two compositions (Each ml of concentrate contains 25 mg of bevacizumab):

- Each 4 ml vial contains 100 mg of bevacizumab

Each 16 ml vial contains 400 mg of bevacizumab

When bevacizumab is used in combination with Lonsurf for the treatment of CRC, the recommended dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks

**3d) Current clinical trials**

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

SUNLIGHT[2] is an open-label, multi-national, randomised, controlled two-arm Phase 3 trial in adults with unresectable, refractory mCRC who had received a maximum of two prior chemotherapy regimens

Between November 2020 and February 2022, 492 patients were enrolled to receive Trifluridine tipiracil + bevacizumab (n=246) or Trifluridine tipiracil monotherapy (n=246).

**3e) Efficacy**

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The combination of trifluridine tipiracil + bevacizumab resulted in a clinically meaningful and statistically significant survival benefit compared to trifluridine tipiracil monotherapy. Trifluridine tipiracil + bevacizumab improved survival by 3.3 months compared to Lonsurf monotherapy 10.8 months with trifluridine tipiracil + bevacizumab vs. 7.5 months with trifluridine tipiracil monotherapy.

Trifluridine tipiracil + bevacizumab resulted in an increase of 3.2 months progression free survival, a greater than two-fold increase versus trifluridine tipiracil monotherapy (5.6 months vs. 2.4 months The probability of being progression-free was consistently higher in patients receiving trifluridine tipiracil + bevacizumab than in patients receiving trifluridine tipiracil monotherapy at 3 months, 6 months, 9 months, and 12 months

**3f) Quality of life impact of the medicine and patient preference information**

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Data were collected from the EORTC QLQ-C30 questionnaire (a cancer-specific QoL measure composed of functional, physical, and global health status [GHS] subscales) and the EuroQol EQ-5D-5L questionnaire (a more general QoL measure, assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and patient's self-rated health.

Cancer-related (QLQ-C30) and general (EQ-5D-5L) HRQoL were maintained for the two patient groups throughout treatment and no clinically relevant changes in scores were observed in any of the sub-domains. Therefore, patients treated with both trifluridine tipiracil + bevacizumab and with trifluridine tipiracil monotherapy did not show increased symptom burden over time

**3g) Safety of the medicine and side effects**

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In SUNLIGHT, adverse events related to the treatment occurred at a higher frequency in the trifluridine tipiracil + bevacizumab group than in the monotherapy group: 90% vs. 81%. Overall, 89.8% of the patients in the combination group and 81.3% in the monotherapy group had AE that were attributed by the investigator to Lonsurf, and 48.4% of the patients in the combination group had bevacizumab-related events

Consistent with previous studies, the most common (>20%)adverse events (related to trifluridine tipiracil and/or bevacizumab) observed in either treatment group were predominantly haematologic and gastrointestinal in nature: neutropenia, anaemia, and nausea.

The most common side effects of Trifluridine tipiracil when used in combination with bevacizumab include: • low blood counts • decreased salt (sodium) in your blood • tiredness and weakness • diarrhea • nausea • stomach-area (abdominal) pain • certain abnormal liver function blood tests • decreased appetite.
Low blood counts are common with and can sometimes be severe and lifethreatening. The medicine can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider may: • lower your dose or stop if you have low white blood cell or low platelet counts.

**3h) Summary of key benefits of treatment for patients**

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Trifluridine tipiracil + bevacizumab establishes a new treatment standard for 3L mCRC patients who received two prior regimens, showing significant and clinically meaningful improvements in survival and progression free survival, while maintaining quality of life and preserving a tolerable safety profile

**3i) Summary of key disadvantages of treatment for patients**

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The bevacizumab component of the treatment requires an intravenous infusion every 2 weeks which requires a hospital visit and can impact on the life of a patient

**3i) Value and economic considerations**

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER). The ICER is measured in terms of the economic value of one additional quality-adjusted life year (QALY) i.e., the costs and benefits of a treatment regimen versus the standard of care (treatments currently used to treat a given condition. The QALY is a measure of disease burden and accounts for both the quality and length of life. A treatment can increase the number of QALYs a patient experiences by extending life, increasing the quality of life, or both. A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

This appraisal estimates the cost-effectiveness of trifluridine-tipiracil plus bevacizumab, versus standard of care treatments which consists of either trifluridine-tipiracil monotherapy, regorafenib or best-supportive care (BSC).

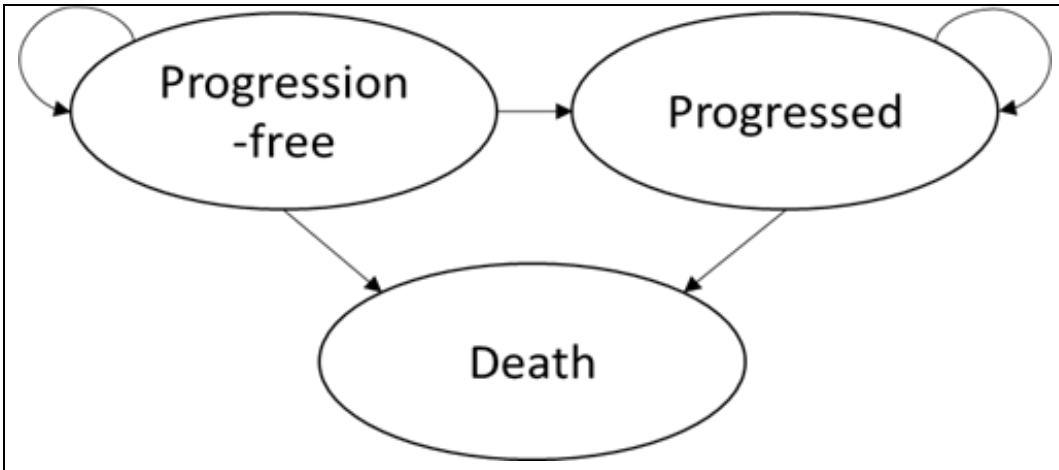
**How the economic assessment of trifluridine-tipiracil with bevacizumab was conducted**

There were no existing economic models which assess the costs (or cost-effectiveness) of trifluridine-tipiracil with bevacizumab for treating patients with metastatic colorectal cancer after 2 systemic treatments. Therefore, a new economic model was developed for the purpose of this submission.

The model was structured using three 'health states' ('progression-free', 'progressed disease' and 'death' as shown below) which help to capture both the costs to the NHS and the impact on length of life and quality of life, for the average patient with metastatic colorectal cancer after 2 systemic treatments. These health states reflect the natural course of mCRC as the condition develops over time.

The costs captured within the analysis include treatment costs, the cost of administering treatment, the costs of managing adverse events related to treatment, the costs of monitoring patients, subsequent treatment costs and the costs of care at the end of life.

The health effects captured within the analysis are QALYs.




The SUNLIGHT trial outcomes of overall survival (OS), progression-free survival (PFS) feed into the model structure, and these outcomes are extrapolated out beyond the follow-up period of the trial, as is often necessary when estimating the lifetime costs and effects of a new treatment. The trial outcomes provided estimates of PFS and OS for trifluridine-tipiracil with bevacizumab versus trifluridine-tipiracil monotherapy. As there were no data available to inform a direct comparison of trifluridine-tipiracil with bevacizumab to regorafenib and BSC, an indirect treatment comparison (ITC) was performed. An ITC reflects a group of statistical methods that can be used to estimate the comparative effectiveness between treatments when there are no head-to-head trials available. The outcome of the ITC were hazard ratios (an OS and PFS HR for regorafenib versus trifluridine-tipiracil with bevacizumab and an OS and PFS HR for BSC versus trifluridine-tipiracil with bevacizumab). These were applied to the extrapolated PFS and OS outcomes to estimate non-direct comparative estimates within the model.

Overall, the modelled outcomes indicate that trifluridine-tipiracil with bevacizumab increases the amount of time spent alive and time spent in the progression free state, and therefore extends life (OS) by delaying disease progression.

Patient reported health-related quality of life (HRQL) outcomes were also reported in the SUNLIGHT study, which were used to inform health-state utility values within the model. From the outcomes reported, it was shown that patients receiving trifluridine-tipiracil with bevacizumab may have a better HRQL than those treated with other standard of care regimens (HRQL was higher for the combination arm than those receiving trifluridine-tipiracil monotherapy).

Adverse events (AEs) associated with each treatment arm were incorporated in the model with costs and HRQL effects included. These were based on the SUNLIGHT study to inform the trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy arms, while the CORRECT and CONCUR studies were used to inform AEs associated with regorafenib and BSC.

**Uncertainty, assumptions, and limitations**

As with all forms of analyses, assumptions need to be made and limitations should be acknowledged.

Structural assumptions were included within the analysis which relate to components such as the model duration (time horizon) and efficacy assumptions (overall survival etc.).

These were tested in scenario analysis to understand the impact different assumptions had on the model results (i.e., the ICER). In addition to scenario analysis, uncertainty related to parameter inputs was also tested. One-way sensitivity analysis (varying parameters at their upper and lower 95% confidence interval bounds), and probabilistic sensitivity analysis (which randomly samples parameters from within a defined distribution) were conducted.

Several simplifying assumptions had to be made. Mostly, these assumptions related to:

- Duration of the model which was assumed to be 15 years
- Duration of treatment
    - In all instances, it was assumed that patients would only receive the intervention or comparator while progression-free
    - For regorafenib time-on-treatment was assumed equivalent to PFS in the absence of other information
- Subsequent treatments which were the same as those observed from the pooled data from the SUNLIGHT study
- No cost was incurred for the administration of oral treatments (as it was assumed to be captured by routine monitoring costs incorporated within the model)

Limitations within the analysis predominantly relate to the assumptions listed above. Further to this, the lack of direct evidence alongside the need to extrapolate outcomes (from incomplete trial data) are limitations which lead to a level of uncertainty within the model. It is hoped that the scenario analyses conducted help interpret and alleviate such uncertainty.

**Value proposition for trifluridine tipiracil with bevacizumab**

Due to the severity of mCRC, patients suffering from the disease face a poor prognosis with substantially reduced life expectancy versus that of the general population (and with poorer HRQL). In line with the new NICE methods, the severity of the condition was determined by estimating the proportional and absolute QALY shortfall. The shortfall is calculated based on the estimated QALYs of the standard of care treatments in relation to the estimated QALYs of the general population (i.e., those who do not have the disease).

The results of the shortfall estimates indicate that a x1.2 or x1.7 severity weighting should be applicable for outcomes associated with mCRC at this line of treatment (after two systemic treatments). As such, results have been presented which illustrate both a x1.2 and x1.7 severity weighting.

The cost of treatment is increased with trifluridine tipiracil with bevacizumab compared to current treatment. However, due to commercial discounts and Patient Access Schemes (PAS') available to the NHS, the true cost of bevacizumab and regorafenib are unknown and therefore the base case results from the economic model have limited interpretability at this stage and would be subject to further evaluation from the NICE team. In order to fulfil our commitment to ensuring that patients can have access to trifluridine tipiracil with bevacizumab, Servier already has an approved PAS in place for trifluridine tipiracil in other indications. This PAS remains relevant for this indication and Servier hope that this will ensure that the combination of trifluridine-tipiracil will be

considered both a clinically effective, and cost-effective treatment option for patients with previously treated metastatic colorectal cancer.

### 3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

This combination brings about a step change to the care pathway for metastatic CRC patients in order to add those valuable extra months to life. The proposed place in therapy of trifluridine-tipiracil plus bevacizumab is alongside trifluridine-tipiracil monotherapy and regorafenib, where trifluridine-tipiracil in combination with bevacizumab has been awarded a score MCBS 4, higher than any of the other treatments available at 3rd line in the most recent update to the ESMO guidelines.

Patients now have an opportunity to benefit from a combination treatment that is highly effective (an additional 3.3 months compared to trifluridine-tipiracil monotherapy) with a favourable safety profile and a positive QoL impact

### 3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:
N/A

## **SECTION 4:** Further information, glossary and references

### 4a) Further information

| Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.<br>Where possible, please provide open access materials or provide copies that patients can access. |
|---|
| Further information on NICE and the role of patients:<br>• Public Involvement at NICE Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance \| Help us develop guidance \| Support for voluntary and community sector (VCS) organisations \| Public involvement \| NICE and the public \| NICE Communities \| About \| NICE<br>• EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/<br>• EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf<br>• National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/<br>• INAHTA: http://www.inahta.org/<br>• European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf |

**4b) Glossary of terms**

| Glossary of terms described throughout document |
|---|
| |

**4c) References**

| Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text: |
|---|
| 1. Cancer Research UK. Bowel cancer statistics. [Internet]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-Zero<br><br>2. Prager GW, Taieb J, Fakih M, Ciardiello F, Van Cutsem E, Elez E, et al. Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med. 2023;388(18):1657–67. |

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

# Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

## Clarification questions

**January 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID6298 trifluridine-tipiracil CRC_clarification questions** | **0.2** | **No** | **05.01.24** |

**Notes for company**

**Highlighting in the template**

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

**To delete grey highlighted text, click anywhere within the text and press DELETE.**

# Section A: Clarification on effectiveness data

## *Systematic literature review*

**A1. Document B, section B.2.1 and Appendix D:** The date of searching of the databases is reported as February 10, 2023 in the 'Identification and selection of relevant studies' section of Document B, which refers to Appendix D for further information. However, the database searches reported in Appendix D were conducted on October 12, 2023, with different results from the earlier search (as evidenced by the respective PRISMA flow diagrams). In addition, the 'version history' of Appendix D (page 3) reports version 4 as "*updated database searches (October 12, 2023) and incorporated new data into NMA*". There appears to be no mention of

an updated search in Document B. Please clarify which search is relevant to the submission and which data were included in the NMA.

The searches were initially carried out on February 10, 2023. However, an updated search was then conducted on October 12 2023 and this is what is provided in the Appendix D. Document B describes the NMA from the initial searches on February 10, 2023 and therefore needs updating. The NMA results from the latest version (i.e., from searches conducted on October 12, 2023) are presented below in Table 1 - Table 4.

**Table 1: Results of random-effects NMA for OS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | 0.59 (0.43,0.79) | 0.6 (0.38,0.95) | 0.41 (0.28,0.58) |

**Table 2: Results of fixed-effects NMA for OS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | 0.59 (0.49,0.73) | 0.59 (0.44,0.79) | 0.42 (0.33,0.53) |

**Table 3: Results of random-effects NMA for PFS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | 0.46 (0.34,0.64) | 0.49 (0.31,0.84) | 0.21 (0.14,0.31) |

**Table 4: Results of fixed-effects NMA for PFS based on constant HRs**

| | Trifluridine-tipiracil | Regorafenib | Placebo/BSC |
|---|---|---|---|
| Trifluridine-tipiracil + bevacizumab | 0.45 (0.38,0.54) | 0.46 (0.35,0.60) | 0.21 (0.17,0.26) |

The NMA included in the economic analysis and model used the results from initial searches conducted on February 10, 2023. These have subsequently been amended to include the results from the updated searches conducted on October 12, 2023 presented above. These can be applied in the revised economic model on the "Controls" sheet in row 79.

The revised results are presented below in Table 5 - Table 7, and results are very similar to those in the original submission. Please note that the company's base case now considers the latest NMA results as presented below and all subsequent scenarios presented within this document include this amendment.

**Table 5: Base case results – pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7)**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 6: Base case results – incremental analysis (with PAS) – 1.2x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.42 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.24 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.07 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.39 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 7: Base case results – incremental analysis (with PAS) – 1.7x severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC(£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.42 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.33 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.10 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.55 | [redacted] | [redacted] |

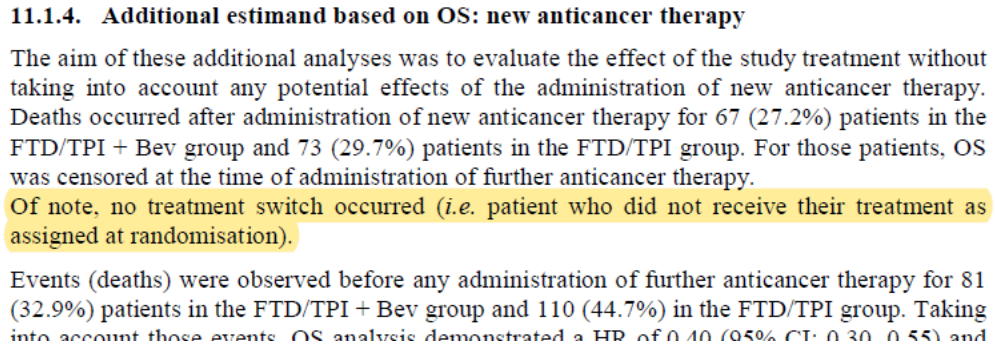
**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

### *SUNLIGHT study design*

**A2. Document B, section B.2.3.2, page 43:** In describing the study design of SUNLIGHT, the CS states "*During the study, administration of further anti-cancer therapy, treatment discontinuation or treatment switching between the two study arms could have occurred*". Please clarify how many participants switched treatment arms and the direction of the switching. Please also clarify whether the impact of treatment switching was considered in the economic model.

According to the CSR, there was no case of treatment switching that occurred. For convenience, a screenshot of the CSR, referring to Section 11.1.4 has been included below in Figure 1.

**Figure 1: Section 11.4.1 from CSR**



**11.1.4. Additional estimand based on OS: new anticancer therapy**

The aim of these additional analyses was to evaluate the effect of the study treatment without taking into account any potential effects of the administration of new anticancer therapy. Deaths occurred after administration of new anticancer therapy for 67 (27.2%) patients in the FTD/TPI + Bev group and 73 (29.7%) patients in the FTD/TPI group. For those patients, OS was censored at the time of administration of further anticancer therapy.

Of note, no treatment switch occurred (*i.e.* patient who did not receive their treatment as assigned at randomisation).

Events (deaths) were observed before any administration of further anticancer therapy for 81 (32.9%) patients in the FTD/TPI + Bev group and 110 (44.7%) in the FTD/TPI group. Taking into account those events, OS analysis demonstrated a HR of 0.40 (95% CI: 0.30, 0.55) and

**Source:** SUNLIGHT CSR[1]

## Section B: Clarification on cost-effectiveness data

### *Treatment effectiveness estimates for use in the economic model*

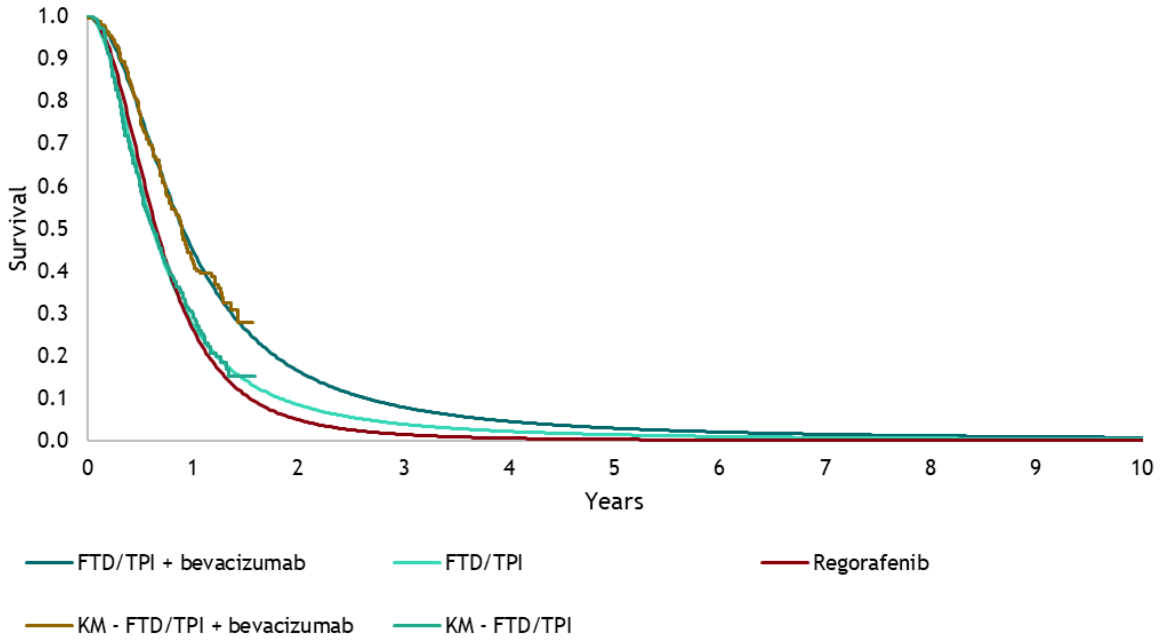
**B1. Document B Section 3.3.2.1, Page 103:** Given that the hazard ratios (HRs) of overall survival (OS) for trifluridine-tipiracil plus bevacizumab compared to both trifluridine-tipiracil monotherapy and regorafenib are very similar, please comment on the plausibility of the longer term modelled OS benefit for trifluridine-tipiracil monotherapy compared to regorafenib.

The modelled long-term estimates of OS show similar outcomes between trifluridine-tipiracil monotherapy and regorafenib (Figure 2) which is consistent with the outcomes of the NMA which report similar HRs of trifluridine-tipiracil monotherapy and regorafenib. There are slight differences in the modelled outcomes between 1

and 3 years which are a result of the different approaches taken to model each treatment. Regorafenib uses the HR from the NMA applied to the trifluridine-tipiracil plus bevacizumab curve assuming proportional hazards, whereas trifluridine-tipiracil monotherapy uses parametric curves independently fitted to the trifluridine-tipiracil monotherapy arm of the SUNLIGHT study. Overall, the similarity in the modelled outcomes appears plausible and is in line with previous clinical considerations.

The previous technology appraisal for regorafenib (TA866), final appraisal documentation notes how a previously conducted NMA and matching-adjusted indirect comparison (MAIC) show similar efficacy between the two treatments.[2] Further to this, the clinical experts in TA866 noted that there may be an additional benefit when using trifluridine-tipiracil monotherapy in this population. Overall the committee considered that regorafenib is 'likely to provide similar benefits' with regard to OS outcomes versus trifluridine-tipiracil monotherapy.[2] These committee and clinical considerations seem aligned with the modelled outcomes below (presented in Figure 2) which project very similar outcomes for regorafenib and trifluridine-tipiracil monotherapy, with slightly favourable OS for trifluridine-tipiracil. As such, Servier consider the comparative modelled outcomes plausible. Scenarios exploring alternative approaches to model regorafenib and trifluridine-tipiracil monotherapy are presented in response to B2 below.

**Figure 2: Modelled OS estimates**




**Key:** FTD/TPI, trifluridine-tipiracil; KM, Kaplan-Meier; OS, overall survival

**B2. <u>PRIORITY.</u> Document B Section 3.3.2, Page 99-111 (regorafenib data included in the model):** Please clarify whether it was possible to obtain any OS, progression free survival (PFS) or time on treatment (TOT) Kaplan-Meier (KM) data, or curves that could be digitised, to allow fitting of survival models directly to regorafenib data? If so, please provide further details and include these as modelling options.

OS, PFS and ToT Data from the regorafenib appraisal TA866, where the company pooled the CORRECT and CONCUR studies, were redacted in the company submission and therefore are unable to be used to inform this scenario. However, Kaplan-Meier data of OS and PFS is published from the CORRECT study.[3] Therefore, for this scenario, these data have been used to inform the regorafenib arm of the model and is naïvely compared against trifluridine-tipiracil plus bevacizumab.

Details of the curve fits have been provided in the appendix at the end of this document. Results of this scenario are presented below in Table 8 and can be applied within the model in the "Controls" sheet row 86. In this scenario, regorafenib's total QALYs have reduced from 0.56 to 0.53 and therefore, a x1.7

severity modifier is still considered the most relevant weighting. Please note that although similar to the NMA modelled outcomes, this approach is a naïve exploratory scenario which uses the replicated data from the CORRECT study without any adjustments.

**Table 8: Scenario pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – regorafenib informed by the CORRECT study**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.79 | 0.53 | [redacted] | 0.56 | 0.41 | 0.49 | 0.70 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

Assuming that the noted data above are not available, please provide the following additional scenario analyses:

- Use OS and PFS HRs obtained from the NMA for both trifluridine-tipiracil monotherapy and regorafenib.
- Set OS and PFS for regorafenib equal to OS and PFS for tipiracil monotherapy.

Please also comment on whether the above analyses have any implications for the calculated quality-adjusted life year (QALY) severity weights.

The scenarios using the HRs from the NMA for both trifluridine-tipiracil monotherapy and regorafenib and assuming equal efficacy are presented below in Table 9 and Table 10, respectively. Using the HRs from the NMA to inform trifluridine-tipiracil monotherapy efficacy reduces the total QALYs of trifluridine-tipiracil slightly from 0.62 to 0.55. This in turn, means that the trifluridine-tipiracil monotherapy comparison would meet the requirement for the for the x1.7 incremental QALY modifier. Currently, using the baseline age and gender split, 0.62 total QALYs corresponds with a 11.39 absolute shortfall and a 94.84% proportional shortfall (which is very close to the cut-off of 95% for the x1.7 modifier). To be eligible for the x1.7 modifier, total QALYs for this population would need to be <0.60. Therefore, the first scenario presented indicates that a x1.7 weighting would be applicable for all comparators to trifluridine-tipiracil plus bevacizumab. Assuming regorafenib has the same efficacy as trifluridine-tipiracil monotherapy increases the total base case regorafenib QALYs from 0.56 to 0.62.

These scenarios can be applied in the model in the “Controls” sheet in rows 82 and 84.

**Table 9: Scenario pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – using HRs for both trifluridine-tipiracil monotherapy and regorafenib**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.82 | 0.55 | [redacted] | 0.53 | 0.39 | 0.47 | 0.67 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 10: Scenario pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – assuming regorafenib OS and PFS is same as trifluridine-tipiracil**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**B3. Economic model, Tab: "Efficacy":** The EAG note that the base case model configuration includes some minor crossing of the selected PFS and TOT curves for trifluridine-tipiracil (FTD/TPI). Please comment on the plausibility that any proportion of patients, even small, might remain on treatment post progression. Please also provide details of the numbers and reasons for treatment discontinuation in both arms of the trial.

Servier do not believe there is any reason why patients will remain on treatment post progression as there are other options following FTD/TPI, as evidenced by the treatment pathway in figure 5 document B

License off treatment post progression

**Figure 3: UK mCRC schematic treatment management**

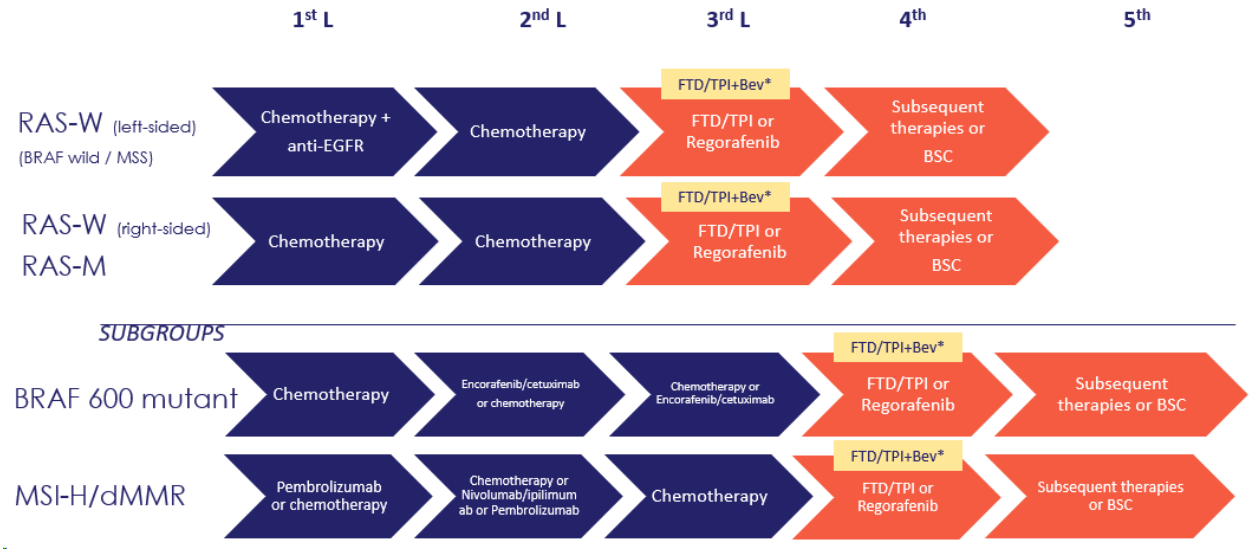



Figure adapted from NICE guidance and feedback of mCRC Therapy Area Experts.[4,5]
Chemotherapy can be FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5-FU, oxaliplatin/ irinotecan).
**Key:** BSC, Best Supportive Care; FTD/TPI+Bev, trifluridine/tipiracil + bevacizumab

It is not plausible that patients might remain on treatment post progression as per the trifluridine-tipiracil license and SUNLIGHT protocol which states that treatment is given until disease progression or unacceptable toxicity.[1,6]

Although the extrapolations of PFS and ToT may cross, to ensure this does not occur in the model (as a result of modelling PFS and ToT separately), ToT is capped

by PFS (applied within the “P-Flow” sheets), so that ToT can never exceed PFS (in line with the license and expected use within practice). This capped approach means that there is no occurrence of PFS and ToT crossing which feed into the modelled outcomes. The resulting curves after capping which inform model results can be found on the “Validation” sheet.

Treatment discontinuation can be found in Table 10.1 of the CSR and is also provided below in Table 11.

**Table 11: Overall disposition of patients from SUNLIGHT**

**Table (10.1) 1 - Overall disposition of patients as of clinical data cut-off 05 July 2022 in the FAS (N = 492)**

| STATUS | | FTD/TPI + Bev (N = 246) | FTD/TPI (N = 246) | All (N = 492) |
|---|---|---|---|---|
| **INCLUDED / RANDOMISED** | n | 246 | 246 | 492 |
| In conformity with the protocol | n (%) | 221 (89.84) | 220 (89.43) | 441 (89.63) |
| With protocol deviation(s) before or at inclusion | n (%) | 25 (10.16) | 26 (10.57) | 51 (10.37) |
| **CONTINUING ON STUDY TREATMENT** | n (%) | 32 (13.01) | 4 (1.63) | 36 (7.32) |
| **WITHDRAWN ON TREATMENT DUE TO** | n (%) | 214 (86.99) | 242 (98.37) | 456 (92.68) |
| Adverse event | n (%) | 16 (6.50) | 16 (6.50) | 32 (6.50) |
| Radiological progressive disease | n (%) | 145 (58.94) | 146 (59.35) | 291 (59.15) |
| Clinical progressive disease | n (%) | 20 (8.13) | 20 (8.13) | 40 (8.13) |
| Radiological and clinical progressive disease | n (%) | 26 (10.57) | 52 (21.14) | 78 (15.85) |
| Non-medical reason: | n (%) | 5 (2.03) | 8 (3.25) | 13 (2.64) |
| Consent withdrawal from study treatment period only | n (%) | 3 (1.22) | 4 (1.63) | 7 (1.42) |
| Consent withdrawal from study treatment period and survival follow-up | n (%) | 2 (0.81) | 4 (1.63) | 6 (1.22) |
| Other, physician decision | n (%) | 2 (0.81) | - | 2 (0.41) |
| **WITHDRAWAL ON TREATMENT RELATED TO COVID-19 PANDEMIC** | n (%) | 3 (1.22) | 3 (1.22) | 6 (1.22) |
| **WITHDRAWN ON FOLLOW-UP PERIOD DUE TO** | n | 145 | 169 | 314 |
| Consent withdrawal | n (%) | 2 (1.38) | 2 (1.18) | 4 (1.27) |
| Lost to follow-up | n (%) | 1 (0.69) | 1 (0.59) | 2 (0.64) |
| Death | n (%) | 142 (97.93) | 166 (98.22) | 308 (98.09) |
| **REASON OF DEATH ON FOLLOW-UP PERIOD** | n | 142 | 166 | 308 |
| Progressive disease | n (%) | 133 (93.66) | 154 (92.77) | 287 (93.18) |
| Other | n (%) | 9 (6.34) | 12 (7.23) | 21 (6.82) |
| **WITHDRAWAL ON FOLLOW-UP RELATED TO COVID-19 PANDEMIC** | n (%) | - | 1 (0.59) | 1 (0.32) |

*N: Number of patients by arm; n: number of patients; Percentages are based on n*

**Key:** FAS, full analysis set; FTD/TPI, trifluridine-tipiracil

**Source:** SUNLIGHT CSR[1]

## *Health related quality of life*

**B4. PRIORITY. Document B Section B.3.4.1, Page 113, Table 39:** Please expand Table 39 to also report the provided data by treatment arm.

Table 12 presents the summary of utilities from SUNLIGHT split by treatment arm.

**Table 12: Summary of SUNLIGHT utility values by health state (EQ-5D-5L cross-walked to EQ-5D-3L) – split by treatment arm.**

| Health state | Number of patients | Number of observations | Mean (SD) | Median (IQR) |
|---|---|---|---|---|
| **Trifluridine-tipiracil with bevacizumab** | | | | |
| Progression-free | 232 | 1,298 | 0.800 (0.189) | 0.836 (0.692 – 0.986) |
| Progressed | 126 | 143 | 0.729 (0.197) | 0.747 (0.624 – 0.867) |
| **Trifluridine-tipiracil** | | | | |
| Progression-free | 215 | 677 | 0.782 (0.218) | 0.810 (0.694 – 0.985) |
| Progressed | 144 | 161 | 0.679 (0.268) | 0.723 (0.563 – 0.864) |

**Key:** IQR, interquartile range; SD, standard deviation

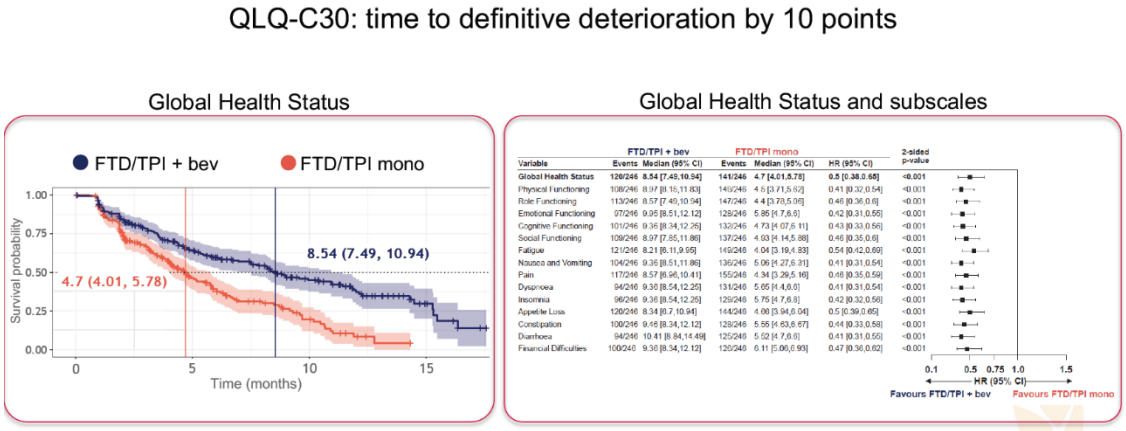
**B5. PRIORITY. Document B Section B.3.4.2, Page 114, Table 40:** Please provide further justification and analyses to support the use of treatment specific health state utility values in the economic model:

- The EAG notes that the detailed results of clinical expert interviews are provided in Appendix N. However, on balance, the expert advice seems to support treatment pooled rather than treatment dependent health state utility values for progressed disease. Please provide a detailed clinical rationale as to why health state utility values might be higher for patients treated with trifluridine-tipiracil with bevacizumab, compared to trifluridine-tipiracil alone, particularly in the progressed disease state of the model.

The clinical experts interviewed as described in Appendix N of the submission dossier, all individually stated that they would expect better quality of life in the trifluridine-tipiracil plus bevacizumab arm in the progression-free state. The rationale for this related to the slower clinical deterioration and improved response rates of trifluridine-tipiracil plus bevacizumab compared to trifluridine-tipiracil monotherapy (ORR 6.1% in the trifluridine-tipiracil plus bevacizumab versus 1.2% in the trifluridine-tipiracil monotherapy group).[1] In the SUNLIGHT trial, the reduced Risk of Deterioration of quality of life favours trifluridine-tipiracil plus bevacizumab vs trifluridine-tipiracil monotherapy based on the “Global

Health Status" scale (Figure 4). In addition, the time to deterioration is longer with trifluridine-tipiracil plus bevacizumab compared to trifluridine-tipiracil monotherapy while considering the QLQ-C30 Global Health Status sensitivity analysis (HR: 0.49, 95% CI: 0.40-0.60 - Figure 5).

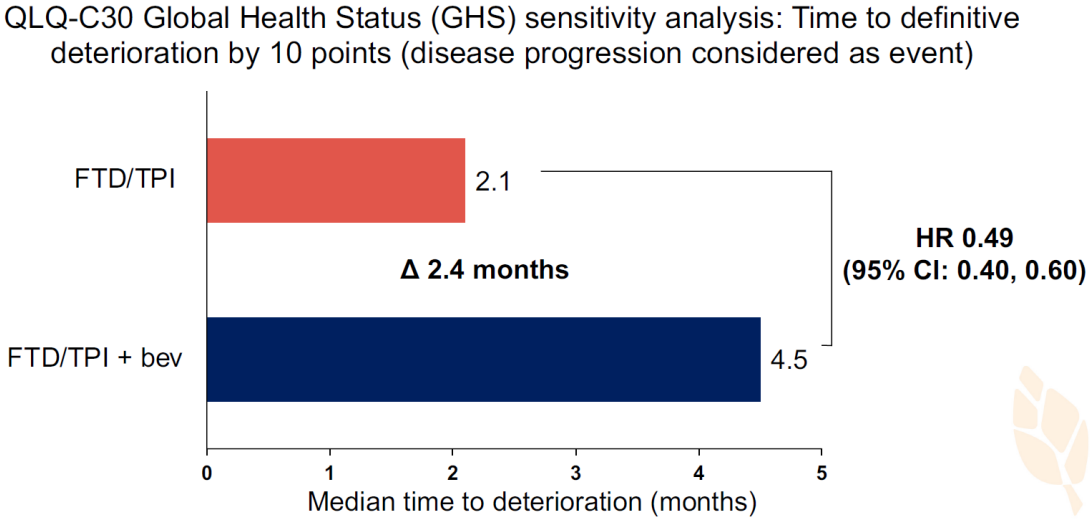
**Figure 4: Risk of Deterioration of quality of life with trifluridine-tipiracil plus bevacizumab**




**Key:** FTD/TPI, trifluridine-tipiracil

**Source:** SUNLIGHT CSR[1]

**Figure 5: Time to deterioration**




**Key:** CI, confidence interval; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio

**Source:** SUNLIGHT CSR[1]

As part of the interviews, some clinical experts also commented that regorafenib may have worse quality of life in comparison to trifluridine-tipiracil

due to increased toxicity and considered that HRQoL would be even lower for BSC patients.

There was uncertainty among the clinicians as to whether a benefit in HRQoL in the PFS state would translate to the progressed state given the lack of evidence in this area. One clinician outlined that a number of things could affect this such as the biology post-progression and next line of treatment. One of the clinicians consulted stated that that there would be a difference in quality of life after progression but that it was likely to be the same after some time. Another clinician believed that quality of life would certainly be different in the progressed state for patients in the regorafenib arm due to ongoing toxicity.

Given the likelihood of better quality of life in the progression-free health state (supported by the HRQoL data collected within the SUNLIGHT study), Servier considers it plausible that the HRQoL benefit would translate to some form of differential HRQoL in the progressed state also. Although progression is defined the same, the higher baseline utilities in a progression-free state would result in a higher quality of life for progressed disease. This is consistent with clinical feedback in prior appraisals.[7,8] Within the economic model, health-state utility values are calculated with the same decline in quality-of-life for progression for all treatment arms (i.e., a deduction of 0.077). This is demonstrated within the SUNLIGHT data which shows that patients on the trifluridine-tipiracil plus bevacizumab arm have a higher utility at their first observation post-progression compared to the trifluridine-tipiracil monotherapy arm (Table 13). Should equal utilities post-progression be assumed, then there would be a larger decrease in HRQoL for patients in the trifluridine-tipiracil plus bevacizumab arm upon progression which lacks validity.

**Table 13: Summary of SUNLIGHT utility values of first observation post-progression (EQ-5D-5L cross-walked to EQ-5D-3L) – split by treatment arm.**

| Treatment arm | Number of patients/ observations | Mean (SD) | Median (IQR) |
|---|---|---|---|
| Trifluridine-tipiracil with bevacizumab | 126 | 0.717 (0.202) | 0.746 (0.621 – 0.860) |
| Trifluridine-tipiracil | 144 | 0.684 (0.256) | 0.723 (0.561 – 0.865) |

**Key:** IQR, interquartile range; SD, standard deviation

Servier agree that post-progression utilities are uncertain and that the difference in patients' quality of life is unknown over time. However, due to the substantial benefit in response rates, it is plausible that patients treated with trifluridine-tipiracil plus bevacizumab have a lower tumour burden upon progression and as such have a better quality of life compared to those patients treated with trifluridine-tipiracil and subsequently regorafenib and BSC.

- please provide a table of key clinical and patient reported outcomes from the trial, stratified by health state and treatment arm to demonstrate whether treatment specific health state utility values are supported by other data from the trial.

  In the SUNLIGHT trial, the EORTC-QLQ-C30 questionnaire was also provided along with the EQ-5D-5L questionnaire within 7 days of randomisation, at day 1 of each cycle prior to any procedure and at study withdrawal. Results of the EORTC-QLQ-C30 patient reported outcomes are presented in Table 14 stratified by health state and treatment arm mapped to the UK values using weights from Norman et al,. 2019.[9] The results are consistent with the EQ-5D utilities showing a higher utility in the progression-free health state for both treatment arms, and a higher utility value for the trifluridine-tipiracil plus bevacizumab arm in both the progression-free and progressed health states compared to trifluridine-tipiracil monotherapy. This is supportive of using treatment specific health state utility values as per the company base case.

**Table 14: Summary of SUNLIGHT utility values by health state (EORTC QLQ-C30) – split by treatment arm.**

| Health state | Number of patients | Number of observations | Mean (SD) | Median (IQR) |
|---|---|---|---|---|
| **Trifluridine-tipiracil with bevacizumab** | | | | |
| Progression-free | 232 | 1,313 | 0.761 (0.201) | 0.816 (0.650 – 0.915) |
| Progressed | 127 | 145 | 0.713 (0.212) | 0.739 (0.580 – 0.857) |
| **Trifluridine-tipiracil** | | | | |
| Progression-free | 216 | 679 | 0.758 (0.193) | 0.812 (0.652 – 0.899) |
| Progressed | 146 | 163 | 0.646 (0.250) | 0.699 (0.477 – 0.824) |

**Key:** IQR, interquartile range; SD, standard deviation

- please provide re-analysis of the trial data using a repeated measures model, including covariates for baseline EQ-5D and an interaction term between health state and treatment in addition to the covariates described in Table 40 (Model 2). Please comment on the most appropriate model for deriving treatment specific health state utility values.

  Table 15 presents the mixed effects regression models including progression and treatment (as previously presented in Document B, Section B.3.4.3) with an additional three models including an interaction term between progression and treatment arm, and a covariate for baseline. These can be summarised as follows:

  - Model 1: mixed effects regression considering only progression status
  - Model 2: mixed effects regression considering treatment arm and progression status – this represents the current model base case
  - Model 3: mixed effects regression considering treatment arm, progression status and an interactive term for the two
  - Model 4: mixed effects regression considering baseline utility, treatment arm, progression status and an interactive term for treatment arm and progression status
  - Model 5: mixed effects regression considering baseline utility treatment arm and progression status

The resulting utilities from the different models are presented in Table 16 and Figure 3. The values from Model 4 and 5 result in a higher progression-free utility value for the trifluridine-tipiracil monotherapy compared to trifluridine-tipiracil plus bevacizumab (0.741 vs 0.745 and 0.744, respectively) which is counterintuitive to the clinical expectation described above (and therefore should be interpreted with caution). The alternative models (Models 1 – 3) have similar values which can be seen in Figure 3, and the addition of the interactive term in Model 3 does not substantially impact the resulting utility values. As such, Servier believe the original base case model (Model 2) to be the most appropriate to inform treatment specific utility values.

**Table 15: Mixed effects regression models**

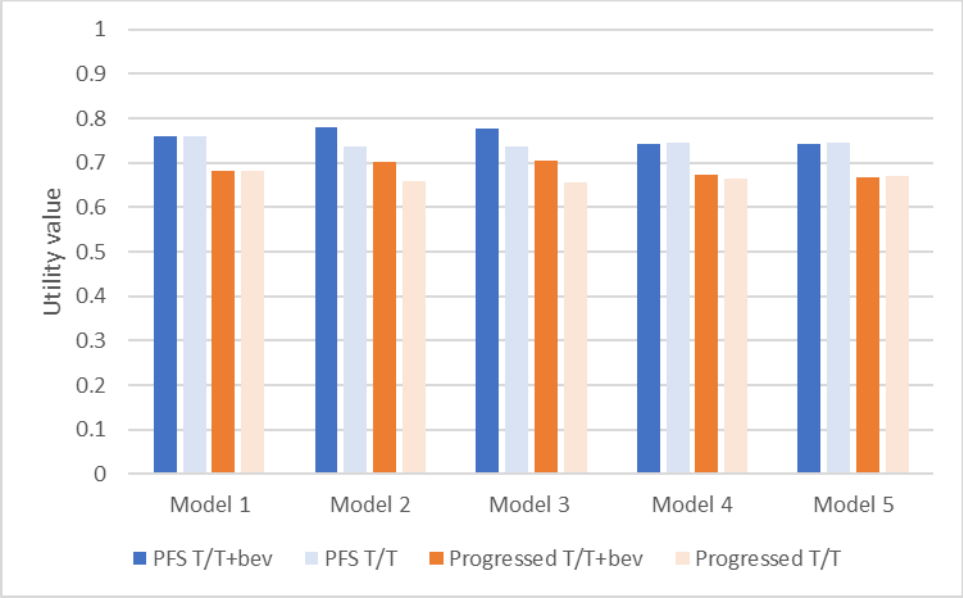
| Coefficient | Value | SE | p-value |
|---|---|---|---|
| **Model 1** | | | |
| Intercept | 0.681 | 0.013 | 0.000 |
| Progression-free | 0.078 | 0.011 | 0.000 |
| **Model 2** | | | |
| Intercept | 0.659 | 0.016 | 0.000 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.043 | 0.018 | 0.021 |
| Progression-free | 0.077 | 0.011 | 0.000 |
| **Model 3** | | | |
| Intercept | 0.655 | 0.182 | 0.000 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.050 | 0.026 | 0.053 |
| Progression-free | 0.082 | 0.015 | 0.000 |
| Interaction term: Treatment arm: Trifluridine-tipiracil plus bevacizumab * Progression-free | -0.009 | 0.022 | 0.670 |
| **Model 4** | | | |
| Intercept | 0.036 | 0.023 | 0.129 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.007 | 0.023 | 0.748 |
| Progression-free | 0.080 | 0.015 | 0.000 |
| Interaction term: Treatment arm: Trifluridine-tipiracil plus bevacizumab * Progression-free | -0.011 | 0.022 | 0.619 |
| Baseline utility | 0.833 | 0.023 | 0.000 |
| **Model 5** | | | |
| Intercept | 0.040 | 0.021 | 0.060 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | -0.003 | 0.010 | 0.755 |
| Progression-free | 0.075 | 0.011 | 0.000 |
| Baseline utility | 0.833 | 0.023 | 0.000 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error

**Table 16: Health state utility values from SUNLIGHT using mixed effects regression models**

| Treatment arm | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| Trifluridine-tipiracil plus bevacizumab | | | | | |
| Progression-free | 0.759 | 0.779 | 0.778 | 0.741 | 0.741 |
| Progressed | 0.681 | 0.702 | 0.705 | 0.672 | 0.666 |
| Trifluridine-tipiracil | | | | | |
| Progression-free | 0.759 | 0.737 | 0.737 | 0.745 | 0.744 |
| Progressed | 0.681 | 0.659 | 0.655 | 0.665 | 0.669 |

**Figure 6: Health state utility values from SUNLIGHT using mixed effects regression models**




**Key:** T/T, trifluridine-tipiracil

**B6. Document B Section B.3.4.4 Table 43:** Several sources have been reported in this table. Please clarify whether the sources of the disutility values adhere to the NICE reference case and are valued using UK population tariffs. Please provide an additional column in the table detailing the utility measurement tool and the value set used for the reported disutilities.

Five key sources from the literature have been used to inform adverse event disutility values in the model, each of which is described in turn below.

- Sullivan et al, 2006[10] provides preference based HRQL scores for clinical classification categories using EQ-5D index scores associated with a variety of chronic diseases. The scoring algorithm for the EQ-5D scores was based on the US community preferences which uses time-trade off to estimate preferences based on a multi-attribute value function.

- Nafees et al, 2008[11] was designed to adapt existing health state descriptions of metastatic breast cancer to describe patients receiving second-line treatment for non-small cell lung cancer (NSCLC). They included symptom burden and the impact of six grade 3-4 toxicities. Preferences for each health state were elicited from a representative group of members of the general public in the UK. The interview included two tasks: the visual analogue scale

(VAS) and Standard Gamble (SG) utility methods; VAS was conducted prior to the elicitation of the health states and SG was used to obtain health state utilities.

- Lloyd et al, 2006[12] was designed to elicit societal preferences for health states describing different metastatic breast cancer disease states in addition to five different grade 3-4 toxicities. VAS and SG utility methods were used to elicit participants' utilities for the health states from a sample of the UK population.

- Doyle et al, 2008[13] was designed to elicit utility values for health state descriptions of patients with metastatic NSCLC with different symptoms and treatment strategies. Members of the UK public completed the standard gamble interview which included a VAS assessment of health states followed by the standard gamble method.

- Hunter et al, 2015[14] presents the results of a cost-effectiveness model of near patient C-reactive protein tests for respiratory tract infections for NHS England. The utility values used in this analysis were used to estimate a disutility of a pulmonary embolism by calculating the different between a healthy utility value and the utility value for respiratory tract infection. The healthy state utility was taken from general population UK utility values from Kind et al, 1999 using EQ-5D values.[15] The respiratory tract infection utility value was taken from another cost-effectiveness study.

The majority of sources used to inform disutilities are based on UK population preferences using a choice-based method consistent with the NICE reference case.[16] In addition to this, several of these studies have also been used in previous appraisals, including in an mCRC setting.[2] Although the utilities have been derived for different disease areas, the quality of life impacts from adverse events are likely to be similar across metastatic disease areas and therefore appropriate to inform disutility values for this appraisal when there is lack of data specific to mCRC.

### *Costs*

**B7. Document B Section B3.5.1.1, Page 125:** The EAG notes that the company have assumed that the relative dose intensity (RDI) for regorafenib is equal to

trifluridine-tipiracil monotherapy, with a scenario analysis exploring the impact of using the regorafenib RDI from the CORRECT study. Please provide further justification for applying an assumption in the base case as opposed to using the available data from the CORRECT study.

Given the similarity in outcomes between regorafenib and trifluridine-tipiracil monotherapy, it is expected that the RDI would be similar between the two arms therefore the same RDI was assumed in the base case. This is also consistent with assumptions made in previous mCRC appraisals. In the prior regorafenib appraisal TA866[2], the company was criticised for assuming different RDI for regorafenib and trifluridine-tipiracil. This was due to a large observational study by Nakashima et al,. 2020 directly comparing the efficacy and safety of regorafenib and trifluridine-tipiracil, which suggests similar dose reductions for both treatments (54% and 48% respectively).[17] As such the EAG for TA866 preferred to assume equal RDIs for regorafenib and trifluridine-tipiracil and the committee concluded that they preferred the EAGs approach.[2]

**B8. Document B Section B3.5.1.2, Page 127 & Economic model file, tab: "costs", cell reference: "N62:N64".** For all treatments in the model, administration costs are based on the cost of a 'first attendance' which was then applied for each subsequent dose in the model (e.g., every two weeks for bevacizumab). What is the justification for not using the unit cost of subsequent attendances? Please provide the results of a scenario analysis that includes 'subsequent attendance' unit costs for treatment administration.

'SB15Z – Deliver subsequent elements of a chemotherapy cycle' is defined in the National Tariff Payment System as *"Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, for example day 8 of a day 1 and 8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen."*[18] As such, this cost should only be applied to the second dose within a treatment cycle and not on the dose received on day 1. Bevacizumab is administered every 2 weeks, therefore Servier considered this to be day 1 of a 14-day cycle and therefore applied the 'Deliver Simple Parenteral Chemotherapy at First Attendance' administration cost every two weeks.

Taking bevacizumab as part of the 28-day cycle length of trifluridine-tipiracil would result in bevacizumab being given on day 1 and day 15 of the 28-day cycle length and therefore the ‘day 15’ administration could be considered appropriate for the SB15Z administration cost. A scenario using SB15Z on the ‘day 15’ administrations of bevacizumab has been included in the model. Note that this does not impact any of the subsequent treatments, all of which have administrations on ‘day 1’ of each treatment cycle.

NHS England provided their budget impact submission for trifluridine-tipiracil plus bevacizumab which used SB12Z for the ‘day 1’ administration and SB15Z for the ‘day 15’ administration based on costs reported in the 2023/25 NHS Payment Scheme.[19] The resulting administration cost is £167 for day 1 and £334 for day 15. For this scenario, the NHS Payment Scheme administration costs are used for all treatment administrations (including subsequent treatments) with the added amendment of including SB15Z for the ‘day 15’ bevacizumab administration.

Results of this scenario are presented in Table 17 and can be applied in the model on the “Costs” sheet in row 90.

**Table 17: Scenario pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – using administrations as per NHS Payment Scheme including 'subsequent attendance'**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**B9. Document B Section B.3.5.2, Table 51, Page 128.** The costs of BSC in the progression free health state are assumed to be minimal (£1.44). Given that there are no treatment acquisition costs included in the model for BSC (e.g., concomitant treatments), can the company please confirm that the modelled BSC costs include all resource use likely to be incurred due to concomitant treatments, monitoring and management of symptoms in UK clinical practice? Has any expert advice been sought regarding the plausibility of the modelled BSC costs in UK clinical practice? If so, please provide further details.

Servier acknowledge that there may be some costs incurred by BSC patients for concomitant medicines, however the costs of these treatments are likely to be small and could be accounted for in all treatment arms. Therefore, it was conservatively assumed that the incremental BSC costs have been captured within resource use. This is also the approach used in prior NICE appraisals in mCRC.[2,20]

In TA866, the company assumed BSC costs to be £0 as they would have been captured in resource use costs.[14] The EAG requested an analysis including BSC costs, however the company was unable to perform a costing exercise for the UK and instead performed a pragmatic scenario analysis assuming a BSC cost of £50 per 28-day cycle. Including these costs had negligible effect on the cost-effectiveness results. The EAG was satisfied with the analysis and agreed that the company's base case assuming zero costs was conservative.

As Servier are also unable to perform a costing analysis to inform BSC costs, the same scenario has been conducted as per the TA866 appraisal. In this scenario, an additional cost of £12.50 per weekly model cycle (£50 per 28-days in line with TA866) is applied in the BSC arm to all patients who are progression-free.

Results of this scenario are presented in Table 18 and can be applied in the model on the "Costs" sheet row 92.

**Table 18: Scenario pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7) – inclusion of BSC costs**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | No weight | x1.2 | x1.7 | No weight | x1.2 | x1.7 |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

### *Base case results*

**B10. Document B Section B3.10, Tables 64 and 65, page 159.** Please clarify how the severity weighting has been applied within the fully incremental analysis. Please also recreate tables 64 and 65 without applying the severity weighting.

At the decision problem meeting stage for this appraisal, the NICE team, the EAG and Servier discussed the limitations of presented incremental analysis when multiple different severity weightings may be considered. As such, it was agreed to present the incremental analysis at both the x1.2 and x1.7 severity weighting. These were presented as follows:

- Table 64 presents incremental analysis applying the x1.2 weighting to all incremental QALYs
- Table 65 applies the x1.7 weighting to all incremental QALYs

Table 19 (below) presents the incremental analysis applying no severity weighting as requested. However, Servier should note that all treatments qualify for a severity modifier (see Document B, Section B.3.6), and therefore Servier considers that interpretation of this incremental analysis should not factor into decision making.

As noted in Section B.3.6, both BSC and regorafenib quality for a x1.7 severity modifier whereas trifluridine-tipiracil qualifies for the x1.2 severity modifier. However, it must be noted that with the total QALYs of 0.62, this is very close to the cut-off required to meet the x1.7 threshold (0.60 QALYs as outlined in the response to B.2). Given two standard of care treatments meet the x1.7 and one is close the threshold, Servier believe that the most appropriate severity weighting for this appraisal would be the x1.7, and that any blended approach would result in a x1.7 weighting. As such, Servier believe that the most relevant incremental analysis is Table 65 in the submission dossier (revised in Table 7 following the updated NMA in the base case) using the x1.7 severity modifier.

**Table 19: Base case results – incremental analysis (with PAS) – No severity weighting**

| Technologies | Total | | Incremental | | ICER versus BSC (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | |
| BSC | [redacted] | 0.42 | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.20 | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.06 | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.32 | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

# Section C: Textual clarification and additional points

## *Information missing from the SUNLIGHT CSR*

**C1. Servier SUNLIGHT CSR:** Please provide Section 15 of the CSR, which is referred to by Sections 11 (efficacy results) and 12 (safety results) of the CSR but is missing from the submitted version.

Attached

## *Publications missing from the reference pack*

**C2. Document B, references:** Please provide copies of references number 51, 52, 53 and 54, which refer to studies included in the network meta-analysis and are currently missing from the reference pack.

Attached

## *Clarifications regarding text in the company submission*

**C3. Document B, Section 3.4.1, Page 113, Table 39:** Please clarify what is meant by the column 'Median (95% CI)'. Are the reported data for the CI referring to percentiles of the distribution?

The '95% CI' is referring to the 25% and 95% percentiles from the median.

**C4. Document B, Section 3.4.5, Page 120, Table 45:** The utility values for PFS and progressed disease appear to be equal for regorafenib and BSC**.** Please check this and update the table with the corrected values if needed.

This is an error in the reporting of this table. The table below has the corrected values (Table 20). This is only an error in the reporting and not within the economic model and therefore does not impact results.

**Table 20: Summary of utility values for cost-effectiveness analysis**

| State | Treatment | Utility value | 95% confidence interval | Reference in submission | Justification |
|---|---|---|---|---|---|
| Base case | | | | | |
| Progression-free: (SUNLIGHT) | Trifluridine-tipiracil + bevacizumab | 0.779 | 0.746 - 0.813 | B.3.4.2 | Derived from SUNLIGHT study |
| | Trifluridine-tipiracil | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| | Regorafenib | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| | BSC | 0.737 | 0.712 - 0.762 | B.3.4.2 | |
| Progressed disease (SUNLIGHT) | Trifluridine-tipiracil + bevacizumab | 0.702 | 0.662 - 0.742 | B.3.4.2 | |
| | Trifluridine-tipiracil | 0.659 | 0.628 - 0.691 | B.3.4.2 | |
| | Regorafenib | 0.659 | 0.712 - 0.762 | B.3.4.2 | |
| | BSC | 0.659 | 0.712 - 0.762 | B.3.4.2 | |
| **Scenario analysis 1** | | | | | |
| Progression-free: (SUNLIGHT pooled) | All | 0.759 | 0.734 - 0.785 | B.3.4.2 | Exploration of uncertainty using pooled treatment utilities from SUNLIGHT trial |
| Progressed disease (SUNLIGHT pooled) | All | 0.681 | 0.655 - 0.707 | B.3.4.2 | |
| **Scenario analysis 2** | | | | | |
| Progression-free: (TA866)[2] | All | 0.72 | 0.71 - 0.73 | B.3.4.3.2 | Exploration of uncertainty using previous TAs |
| Progressed disease (TA866)[2] | All | 0.59 | 0.56 - 0.62 | B.3.4.3.2 | |
| **Scenario analysis 3** | | | | | |

| State | Treatment | Utility value | 95% confidence interval | Reference in submission | Justification |
|---|---|---|---|---|---|
| Progression-free: (TA405)[20] | All | 0.73 | 0.71-0.75 | B.3.4.3.2 | Exploration of uncertainty using previous TAs |
| Progressed disease (TA405)[20] | All | 0.64 | 0.62-0.66 | B.3.4.3.2 | |

**Key:** BSC, best supportive care; TA, technology appraisal

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# Appendix: CORRECT study curve fits

In response to clarification question B2, OS and PFS Kaplan-Meier data published from the CORRECT study were digitized and used to create pseudo patient-level data using the Guyot algorithm.[21] Parametric survival models (PSMs) were fitted to OS, and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to inform the model.

AIC and BIC for OS and PSMs are provided in Table 21. Based on the AIC and BIC scores, the log-logistic model provided the best fit for both OS and PFS. Although several of the PSMs have relatively close AIB/BIC statistics to the best fitting curves, some curves indicate a poorer fit with much higher AIC/BIC statistics (e.g., the exponential and Gompertz curves), which could infer a poorer fit for the treatment arms.[22]

**Table 21: Statistical goodness-of-fit scores - CORRECT**

| Parameterisation | Overall survival | | Progression-free survival | |
|---|---|---|---|---|
| | AIC | BIC | AIC | BIC |
| Exponential | 1823.2 | 1827.4 | 1909.8 | 1914.0 |
| Generalised gamma | 1771.8 | 1784.5 | 1766.6 | 1779.3 |
| Gompertz | 1804.9 | 1813.3 | 1890.0 | 1898.5 |
| Log-logistic | **1769.8** | **1778.2** | **1760.6** | **1769.0** |
| Log-normal | 1771.9 | 1780.3 | 1764.6 | 1773.1 |
| Weibull | 1780.7 | 1789.1 | 1829.7 | 1838.2 |

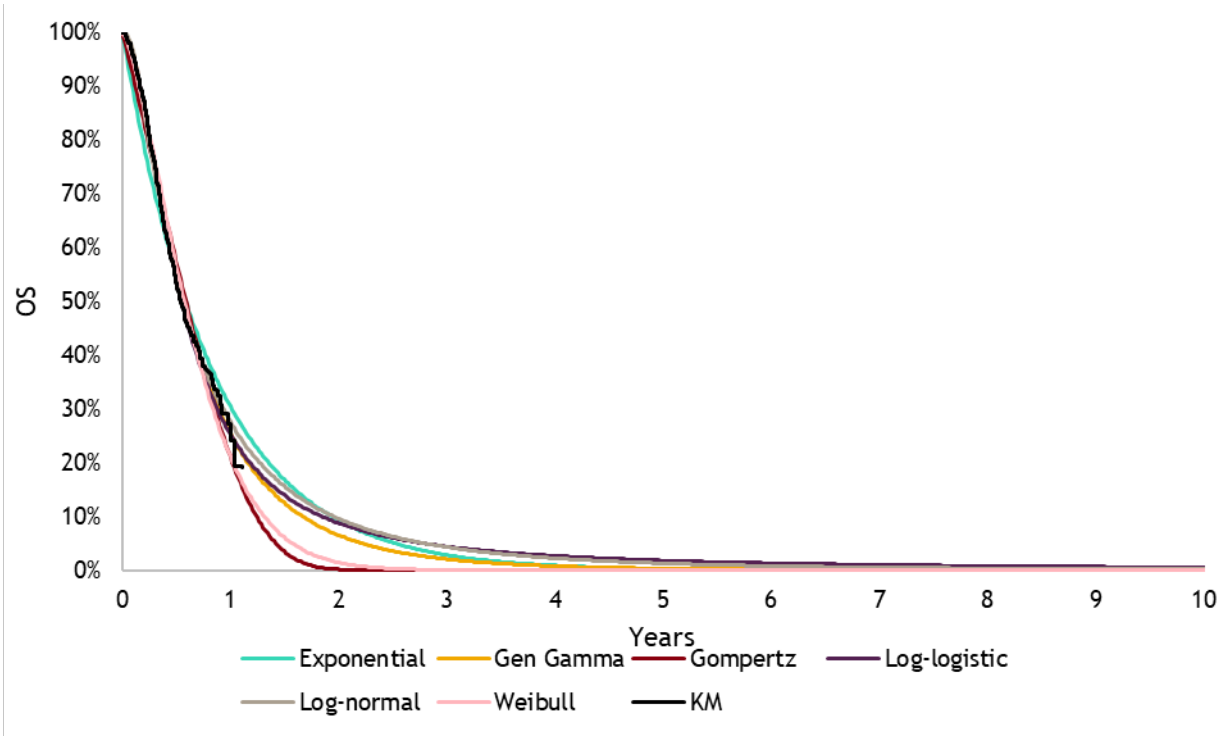
**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 3 and Figure 4 present the OS and PFS PSMs, respectively. For OS, the models appear to fit the data well until around 1 year where Gompertz, Weibull and exponential appear to either underestimate or overestimate the tail of the KM. This leaves generalised gamma, log-normal and log-logistic as more plausible options. Based on the clinical feedback received from clinician experts for trifluridine-tipiracil monotherapy during the original submission (see Document B, Section B.3.3.2.1), who expected between 2-10% alive at 2 years with very few or no patients alive by 5 years, and the likely assumption that regorafenib has similar efficacy, generalised gamma was considered the most plausible estimating 6.6% and 0.3% alive at 2 and 5 years, respectively. Therefore, based on reasonable statistical and visual fit and clinical plausibility, generalised gamma has been used to inform this scenario for

regorafenib. This is also consistent with the OS distribution preferred by the committee for the regorafenib appraisal TA866.[2]

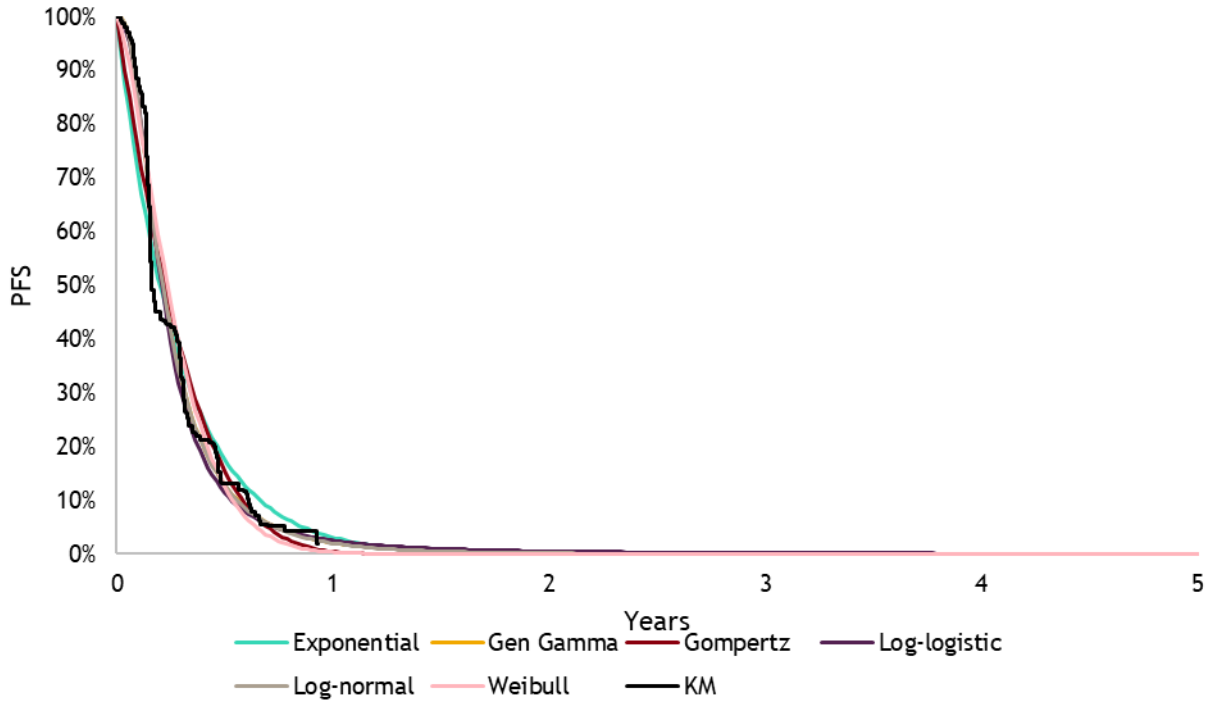
For PFS, all the curves appear to fit the data reasonably well, with some minor under- and overestimating throughout due to 'steps' in the observed data likely caused by the protocol driven assessments of progression. Based on the clinical feedback received from clinician experts for trifluridine-tipiracil monotherapy during the original submission (see Document B, Section B.3.3.2.1), who expected no patients or less than 0.2% at 2 years to be progression-free, log-logistic is not a plausible option which estimates 0.5% progression-free at 2 years. As generalised gamma was the preferred distribution for PFS in TA866, this has been chosen to inform this scenario, however due to the similar projected long-term outcomes between curves, the chosen curve is unlikely to have a large impact on results.

**Figure 7: Parametric curve fits – CORRECT - OS**




**Key:** KM, Kaplan-Meier; OS, overall survival

**Figure 8: Parametric curve fits – CORRECT - PFS**




**Key:** KM, Kaplan-Meier; PFS, progression-free survival

NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

# Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

## About you

| | |
|---|---|
| **1.Your name** | [redacted] |
| **2. Name of organisation** | Bowel Cancer UK |
| **3. Job title or position** | Policy Officer (England) |
| **4a. Brief description of the organisation (including who funds it). How many members does it have?** | We are the UK's leading bowel cancer charity. We are determined to save lives and improve the quality of life of everyone affected by bowel cancer by championing early diagnosis and access to best treatment and care. We support and fund targeted research, provide expert information and support to patients and their families, educate the public and professionals about the disease and campaign for early diagnosis and access to best treatment and care. The majority of our income is generated from individual, corporate and trust fundraisers. A small proportion is given by pharmaceutical and medical device companies in support of patient and healthcare professional education days and award-winning information sources. |
| **4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of the company, amount, and purpose of funding.** | No |

| | |
|---|---|
| **4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |
| **5. How did you gather information about the experiences of patients and carers to include in your submission?** | The information we provide in this response on the experiences of patients was gathered from a survey of people diagnosed with advanced bowel cancer who have undergone two systematic treatments. We posted the survey on our patient online forum for one week and anonymised responses as we received them. |

## Living with the condition

| | |
|---|---|
| **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?** | A bowel cancer diagnosis is life-changing and can affect almost every aspect of daily life, not only for the individual diagnosed but also for their family and loved ones. This is even more acute for those diagnosed at the later stages of the disease, when it is harder to treat, and the chance of survival is lower. Patients experience numerous difficulties and challenges across the pathway, from getting an initial diagnosis to timely treatment and care. These challenges relate to the impact and reality of an advanced bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on quality of life.<br><br>**Patients used words like 'helpless', 'tough', 'hard', and 'extreme' to describe their overall experience living with advanced bowel cancer. Our community told us:** |

| | |
|---|---|
| | *“Living with [stage] 4 bowel cancer is hard on both myself and my family. Mentally it turned my world upside down and it never leaves you and you cannot plan anything more than two months ahead because you bounce from scan to scan. I get extreme anxiety waiting for scans and results.’”*<br><br>*“I often wake up to find my husband crying because he feels helpless. My Mother cannot grasp that I may not be here in six months. I have (luckily) lived this this life for over three years.”*<br><br>*”It has been a tough journey, we are about 5 years on from initial stage 3 diagnosis (after a GP told my husband the first time he went that he should eat better and take charcoal tablets, which made him delay going again).”*<br><br>*“We had to cancel our wedding to start treatment when it moved to stage 4 (once again spread to liver missed by NHS and only picked up when it had spread to lungs too). We also had to give up on our plans to have kids.”*<br><br>**Patients undergoing treatments for advanced bowel cancer experience a range of side effects which significantly affect their quality of life – both physically and emotionally.**<br><br>*“We’ve had to put our lives on hold as my husband struggles with side effects, has nerve pain from Oxaliplatin which was administered via a cannula and caused him severe pain.”*<br><br>*“I now plan my fortnights as having 7 days not feeling great and 7 days relatively normal. I rarely see anybody the first seven days.”*<br><br>*“quality of life isn’t great as chemo impacts his personality.”* |

**Current treatment of the condition in the NHS**

| | |
|---|---|
| **7. What do patients or carers think of current treatments and care available on the NHS?** | Survival for advanced bowel cancer is poor, with only 10.5% surviving more than five years. These patients deserve access to the best quality treatment and care. For some patients these drugs can prolong life, resulting in more time to spend with loved ones. Therefore, it is essential patients gain timely access to the treatments that their clinicians feel could benefit them.<br><br>However, current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited. The impact of this on patients' life expectancy and psychological wellbeing is detrimental, with many patients unable to access a treatment that could prolong their life and give them more time with their loved ones. This has financial implications for patients and their families, with many resorting to fundraising or borrowing money to fund treatments privately. This causes unnecessary stress, worry and anxiety when they are already struggling to come to terms with their diagnosis.<br><br>**Our community told us:**<br><br>*'NHS treatment varies and is a postcode lottery. I see the oncologist 3 times a year and speak to the specialist nurse three times a year. I have a phone number for cancer care hotline and then leave a message on a switchboard. I left a message on 13/3 and never heard again.'*<br><br>*'I cannot email the oncologist or nurse. Generally feel cast aside by them. I have twice turned up for scan results (6 weeks after scans) and they are still waiting. I complained to PALS both times. The whole process makes the disease even harder to cope with.'*<br><br>*'We were on the NHS for his first surgery and round of chemo. There were delays with his surgery (in 2018) due to low availability of scanners, scan advice not arriving and things being pushed out. In the end we went private to speed up access to chemo and to have access to extra treatments (e,g Avastin).'*<br><br>*'The NHS could remove the postcode lottery so that there is one standard of care. Worst still knowing that if I could afford it I would have been offered avastin with Folfiri and others on that are having remarkable success. I sometimes lie in bed crying knowing that it's not for the likes of people on the NHS. In the stage 4 community NHS oncologists suggest crowd funding to pay for it. Even that is a postcode lottery. Depending on your trust it varies from £150 - £2500 per treatment. It is a discussion I'm due to have in the future.'* |

| | |
|---|---|
| **8. Is there an unmet need for patients with this condition?** | There is an unmet need for this specific patient population and all survey responders agreed. There are currently extremely limited treatment options available for people diagnosed with advanced bowel cancer. The evaluation of this technology is vital to increasing available treatments for advanced cancer patients receiving care on the NHS.<br>**Our community told us:**<br>*'It is horrendous that people are being denied a treatment that could provide extra years to them.'*<br>*'NICE need to realise the impact of knowing that there is a drug out in the community that could give me months or even longer and yet it's only for the rich. The sunlight trials have proved this. That is immoral and saying my life isn't worth anything. If my husband does need to raise the mortgage to give me a chance at it then surely the NHS should have it available at the cheapest price to stage four bowel cancer suffers.'*<br>*'For patients like my husband who has a mutation where there is currently no immunotherapy, treatments like Avastin should be funded.'* |

## Advantages of the technology

| | |
|---|---|
| **9. What do patients or carers think are the advantages of the technology?** | Patients and carers support the provision of this technology on the NHS due to its potential to prolong life and reduce disparities in treatment and care.<br>**Our community told us:**<br>*'Before my husband had Avastin added [received trifluridine–tipiracil with bevacizumab], he had new tumours grow in a 2 week period. Following Avastin being added, despite growth when off treatment, it was small growth in 3-6 months and things have slowed down significantly which has given him more time. The additional side effects of Avastin appear to have been minimal. See above re the difference Avastin has made for him specifically. It has bought him time and we remain hopeful that a new therapy will be found for KRAS mutations.'*<br>*'Specifically in my husband's case, Lonsurf and Avastin was the first treatment (he'd been on Folfiri, Capox and Folfox) that had any noticeable impact on his lung mets. After 3 months they had shrunk by about 20-25%. With* |

| | |
|---|---|
| | *small reductions thereafter. A PER scan showed only one met that was active so it was viewed as more than stable. His case was discussed at MDT due to the great outcome for him on this treatment to acknowledge that the combination could be positive for some patients.'*<br><br>*'I strongly believe everybody should have the option of Lonsurf and Avastin not just young people, BRAF, KRAS or RAS.'* |

## Disadvantages of the technology

| | |
|---|---|
| **10. What do patients or carers think are the disadvantages of the technology?** | N/A |

## Patient population

| | |
|---|---|
| **11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.** | N/A |

## Equality

| | |
|---|---|
| **12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?** | N/A |

## Other issues

| | |
|---|---|
| **13. Are there any other issues that you would like the committee to consider?** | N/A |

## Key messages

| | |
|---|---|
| **14. In up to 5 bullet points, please summarise the key messages of your submission.** | • A bowel cancer diagnosis can be life-changing for those diagnosed, as well as their friends and family, and is even more acute for those at later stages of the disease when it is harder to treat and there is a lower chance of survival.<br>• Current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life.<br>• Patients and carers advocated for access to trifluridine–tipiracil with bevacizumab due to its life-prolonging potential.<br>• Patients and carers stressed the impact of a lack treatment options and availability on their mental health during what is already a very difficult and distressing time, explaining that access to this treatment would offer greater hope for their recovery and prolonged survival. |

Thank you for your time.

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# Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

**Produced by** Aberdeen HTA Group

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Leslie Samuel, clinical advisor, declares the following:

- Receipt of an honorarium from Servier for speaking at a UK national colorectal cancer educational meeting in November 2023.
- Institutional funding to NHS Grampian from Servier several years ago as a site for the SOLSTICE clinical trial.
- Institutional funding to NHS Grampian from Hutchison Pharma as a site for the FRESCO-2 clinical trial for Fruquinitinib, where he was the UK CI.
- Receipt of an honorarium from Takeda for an Advisory Board meeting on Fruquintinib.

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**Rider on responsibility for report**

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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**Contribution of authors**

Moira Cruickshank reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; Dolapo Ayansina and Sachin Kumar checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers and Mary Kilonzo reviewed and critiqued the cost-effectiveness evidence and economic model; Paul Manson checked and critiqued the company's search strategies; Leslie Samuel provided clinical guidance and comments on the draft report. Miriam Brazzelli and Dwayne Boyers coordinated all aspects of this appraisal and are the guarantors of this report. All authors contributed to the writing of this report and approved its final version.

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**List of abbreviations**

| Abbreviation | Description |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 3L | Third-line |
| 5-FU | Fluorouracil |
| AE | Adverse events |
| AFT | Acceleration failure time |
| AIC | Akaike information criteria |
| ASCO | American society of clinical oncology |
| BIC | Bayesian information criteria |
| BID | Twice daily |
| BNF | British National Formulary |
| BRAF | V-Raf murine sarcoma viral oncogene homolog B1 |
| BSA | Body surface area |
| BSC | Best supportive care |
| CAPOX | Capecitabine, oxaliplatin |
| CEAC | Cost-effectiveness acceptability curve |
| CENTRAL | Cochrane central register of controlled trials |
| CI | Confidence interval |
| CIMP | CpG island methylator phenotype |
| CIN | Chromosomal instability |
| CR | Complete response |
| CRC | Colorectal cancer |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| DCR | Disease control rate |
| DMMR | DNA mismatch repair |
| DOR | Duration of response |
| DSU | Decision support unit |
| ECOG | Eastern cooperative oncology group |

| Abbreviation | Description |
|---|---|
| EGFR | Epidermal growth factor receptor |
| EMA | European medicines agency |
| EMBASE | Excerpta medica database |
| eMIT | Electronic market information tool |
| EORTC QLQ-C30 | European organisation for the research and treatment of cancer quality of life questionnaire |
| EQ-5D-5L | EuroQol-5 dimension-5 levels |
| ESCAT | Scale for clinical actionability of molecular targets |
| ESMO | European society medical oncology |
| FAS | Full analysis set |
| FDG-PET | Fluorodeoxyglucose-positron emission tomography |
| FOLFIRI | 5-FU, leucovorin, and irinotecan |
| FOLFOX | 5-FU, leucovorin, and oxaliplatin |
| FOLFOXIRI | 5-FU, leucovorin, oxaliplatin, and irinotecan |
| FTD/TPI | Trifluridine-tipiracil |
| GHS | Global health status; |
| HER2 | Human epidermal growth factor receptor 2 |
| HNPCC | Hereditary nonpolyposis colorectal cancer |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| IA | Investigator-assessed |
| ICER | Incremental cost-effectiveness ratio |
| IMP | Investigational medicinal product |
| INMB | Incremental net-monetary benefit |
| IRC | Independent review committee |
| ITT | Intention to treat |
| IV | Intravenous; |
| KM | Kaplan-Meier |
| KRAS | Kirsten Rat sarcoma proto-oncogene GTPase |
| LCHP | Log cumulative hazard plots |
| LYG | Life years gained |

| Abbreviation | Description |
|---|---|
| mAB | Monoclonal antibody |
| MCBS | Magnitude of clinical benefit scale |
| mCRC | Metastatic colorectal cancer |
| MEDLINE | Medical literature analysis and retrieval system online |
| MRI | Magnetic resonance imaging |
| MSI | Microsatellite instability |
| NCC | National cost collection |
| NHB | Net-health benefit |
| NMA | Network meta-analysis |
| NRAS | Neuroblastoma rat sarcoma viral oncogene homolog |
| ONS | Office of national statistics |
| ORR | Objective response rate |
| OS | Overall survival |
| OWSA | One-way sensitivity analysis |
| PartSA | Partitioned survival analysis |
| PAS | Patient access scheme |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PH | Proportion hazards |
| PICOS | Population, interventions, comparators, outcomes, and study design |
| PO | Oral |
| PRISMA | Preferred reporting items for systematic reviews and meta-analyses |
| PR | Partial response |
| PS | Performance status |
| PSA | Probabilistic sensitivity analysis |
| PSM | Parametric survival models |
| PSS | Personal social services |
| PSSRU | Personal social services research unit |
| QALY | Quality-adjusted life years |

| Abbreviation | Description |
|---|---|
| QoL | Quality of life |
| QQ | Quantile-quantile |
| RAS | Rat sarcoma virus |
| RCT | Randomised controlled trial |
| RDI | Relative dose intensity |
| RECIST | Response evaluation criteria in solid tumours |
| SAE | Serious adverse events |
| SD | Standard deviation |
| SS | Safety set |
| SLR | Systematic literature review |
| SmPC | Summary product characteristics |
| TA | Technology appraisal |
| TEAE | Treatment-related emergent adverse events |
| ToT | Time on treatment |
| TP53 | Tumour protein p53 |
| TSD | Technical support document |
| TTD | Time to treatment discontinuation |
| TWiST | Prior to disease progression without adverse events |
| USG | Ultrasonography |
| VEGF | Vascular endothelial growth factor |
| WT | Wild-type |
| WTP | Willingness-to-pay |

# 1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology, and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

## 1.1 Overview of the EAG's key issues

Table 1 describes a summary of the EAG's key issues. For this assessment, key issues identified by the EAG relate to differences of opinion between the company and EAG preferred base cases, rather than an EAG request for further consultation. Indeed, the EAG is satisfied that a detailed evidence submission has been provided by the company and further engagement would be unlikely to reduce uncertainty surrounding the most appropriate ICER for committee.

**Table 1 Summary of key issues**

| ID 6298 | Summary of issue | Report sections |
|---|---|---|
| 1 | The EAG prefers the use of a generalised gamma overall survival model for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy whereas the company prefers a log-logistic. | 4.2.6 |
| 2 | The EAG prefers to estimate regorafenib overall and progression free survival using data from the CORRECT study rather than applying HRs from the company's conducted NMA to an accelerated failure time extrapolation. | 4.2.6 |
| 3 | The EAG prefer to assume that a proportion of the progression free cohort remain on regorafenib treatment at any point in time whereas the company prefer to assume that treatment continues to progression. The EAG's preferred proportion is calculated from modelled mean PFS and mean time on treatment from the CORRECT study. | 4.2.6 |
| 4 | The EAG prefers treatment pooled health state utility values from the SUNLIGHT study, whereas the company prefers treatment dependent utilities. | 4.2.7 |

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are described in Table 1. These differences in opinion are the ones that are most likely to have an important impact on the ICER. Other issues of differing opinion between the company and EAG around regorafenib relative dose intensity, post-progression treatment costs, BSC costs and the use of different price sources do not have a major impact on the ICER, but they require a judgement call from committee about the most appropriate set of preferred assumptions.

## 1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing overall survival,
- Increasing the amount of time patients remain progression free, leading to improvements in quality of life.

Overall, the technology is modelled to affect costs by:

- Leading to treatment acquisition costs for two treatments instead of one.
- Requiring treatment administration costs for intravenous use of bevacizumab
- Increasing both treatment acquisition and administration costs due to longer time on treatment, due primarily to patients achieving a longer time progression free.

The modelling assumptions that have the greatest effect on the ICER are:

- The size of the overall survival benefit for trifluridine-tipiracil + bevacizumab compared to other treatments and assumptions about how best to model longer term survival benefit.
- The most appropriate source of data for overall survival, progression-free survival and time on treatment for regorafenib.

## 1.3 The decision problem: summary of the EAG's key issues

The main deviation from the final scope issued by NICE is that in their submission the company restricted the comparator treatments to trifluridine-tipiracil monotherapy, regorafenib and best supportive care. The EAG's clinical expert considers these comparators appropriate to address the decision problem.

## 1.4 The clinical effectiveness evidence: summary of the EAG's key issues

In the company's submission, the primary evidence for the clinical effectiveness of trifluridine-tipiracil and bevacizumab versus trifluridine-tipiracil monotherapy is based on the SUNLIGHT phase III trial. To compare the effectiveness of trifluridine-tipiracil and bevacizumab with other relevant comparator treatments (placebo/BSC, trifluridine-tipiracil

monotherapy and regorafenib), the company present random-effects and fixed-effects NMAs. showing the superiority of trifluridine-tipiracil and bevacizumab for both PFS and OS. The methodological approach taken by the company for these analyses is appropriate and the EAG has identified no major issues of concern.

### 1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG has identified four key issues of remaining uncertainty that are likely to have an impact on estimates of cost-effectiveness. These are discussed in the following tables.

**Issue 1 Most appropriate overall survival model**

| | |
|---|---|
| **Report section** | 4.2.6 |
| **Description of the issue and why the EAG has identified it as important** | The company and EAG disagree about the most appropriate overall survival curve for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy. This is an issue because it has implications for the magnitude of incremental life year gains, and hence cost-effectiveness estimates. The company prefers to use a log-logistic curve. |
| **What alternative approach has the EAG suggested?** | Several curves offer a good visual and statistical fit to the Kaplan Meier data. The EAG prefers to use a generalised gamma survival curve because it predicts lower longer-term overall survival for both the intervention and comparator that is more in line with the EAG's clinical expert expectations. It also more accurately describes a steep fall in the survival proportion at early points on the curve that would be expected for patients likely to be treated in UK clinical practice. The generalised gamma also predicts a 2-year survival effect size that is more in line with that observed from the available data. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG's preferred approach increases the ICER for trifluridine-tipiracil + bevacizumab compared to trifluridine-tipiracil alone. |
| **What additional evidence or analyses might help to resolve this key issue?** | Any long-term evidence on overall survival for any of the mCRC treatments considered in this assessment would be helpful in deciding on the most appropriate OS curve. |

**Issue 2 Most appropriate approach to modelling regorafenib OS and PFS**

| | |
|---|---|
| **Report section** | 4.2.6 |
| **Description of the issue and why the EAG has identified it as important** | The company and EAG disagree about the most appropriate approach to modelling regorafenib OS and PFS. This is an issue because it has implications for the magnitude of modelled QALY benefits for trifluridine-tipiracil + bevacizumab compared to regorafenib. |
| **What alternative approach has the EAG suggested?** | The company prefer to apply hazard ratios from their network-meta-analysis to the underlying OS and PFS curves for trifluridine-tipiracil + bevacizumab. Both EAG and company preferred OS (generalised gamma and log-logistic) and PFS curves (log normal) are accelerated failure time models that imply violation of the proportional hazard assumption. The EAG therefore prefers to use survival models fitted independently to the observed Kaplan Meier data from the CORRECT study. The EAG's approach implies that a naïve comparison of the studies is plausible, and this generates uncertainty about the most appropriate approach to use. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG's preferred approach reduces costs and QALYs for regorafenib, leading to a moderate increase in the ICER. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG is not aware of any additional evidence that would help resolve this issue. |

**Issue 3 Most appropriate approach to modelling regorafenib time on treatment**

| | |
|---|---|
| **Report section** | 4.2.6 |
| **Description of the issue and why the EAG has identified it as important** | The company and EAG disagree about the most appropriate approach to modelling regorafenib time on treatment. This is an issue because it has implications for the treatment acquisition costs included in the model for regorafenib. |
| **What alternative approach has the EAG suggested?** | The company prefer to assume that regorafenib time on treatment is equal to progression free survival, implying that treatment would never be discontinued prior to progression. The EAG considers the company's approach to over-estimate regorafenib time on treatment, and hence treatment acquisition costs, compared to evidence from the CORRECT study. The EAG and company clinical experts both note concerns about regorafenib toxicity, and it is reasonable to assume that some people may discontinue treatment due to toxicity. The EAG prefers to calculate the proportion of the progression free cohort on treatment using mean time on treatment from the CORRECT study as a proportion of the mean modelled PFS for regorafenib. The approach ensures consistency with the CORRECT study data and maintains consistency of the EAG's preferred data source for regorafenib more generally. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG's preferred approach reduces treatment acquisition costs for regorafenib, thereby leading to a substantial increase in the ICER for trifluridine-tipiracil + bevacizumab compared to regorafenib. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG is aware that treatment discontinuation curves for regorafenib will have been available to committee as part of TA866. If these data were available to committee, they would help reduce uncertainty regarding the most appropriate approach to modelling regorafenib treatment discontinuation. |

**Issue 4 Most appropriate approach to modelling regorafenib time on treatment**

| | |
|---|---|
| **Report section** | 4.2.7 |
| **Description of the issue and why the EAG has identified it as important** | The company and EAG disagree about whether treatment specific or treatment pooled health state utility values should be used in the model. This is an issue because it has implications for the modelled QALY benefits of trifluridine-tipiracil + bevacizumab vs. comparators. |
| **What alternative approach has the EAG suggested?** | The company prefer to apply treatment specific HSUVs, derived from a mixed effects regression model controlling for treatment arm and health state. However, the EAG disagree that the approach is sufficiently supported by the company's evidence. For example, interaction terms between treatment and state included in exploratory regression models are not statistically significant. Furthermore, when adding baseline utility to the company's preferred regression model, the treatment effect is no longer significant. The EAG therefore prefers to use treatment pooled health state utility values. |
| **What is the expected effect on the cost-effectiveness estimates?** | The EAG's preferred approach increases the ICER for trifluridine-tipiracil + bevacizumab vs. comparators because it removes an additional treatment effect within each modelled health state. |
| **What additional evidence or analyses might help to resolve this key issue?** | The EAG is not aware of any additional evidence that would help resolve this issue. |

## 1.6 Summary of EAG's preferred assumptions and resulting ICER

The impact of the EAG's preferred assumptions on the ICER are provided in Table 2 below, changing each assumption from the company's base case one at a time in a fully incremental analysis. Pairwise comparisons are provided in Chapters 5 and 6. Fully incremental ICERs are provided for all severity weightings, thought the EAG notes that in both the company and EAG preferred base case a weighting of 1.2 should be applied to trifluridine-tipiracil with or without bevacizumab, with a 1.7 weighting for regorafenib and BSC.

**Table 2 Summary of EAG's preferred assumptions and ICER**

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Company preferred base case post clarification queries** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 1: Generalised Gamma OS curves for Trifluridine Tipiracil +bevacizumab and Trifluridine tipiracil** | | | | | | | |
| BSC | [redacted] | 0.418 | | | | | |
| FTD/TPI | [redacted] | 0.591 | [redacted] | 0.173 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.537 | [redacted] | -0.054 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.811 | [redacted] | 0.220 | [redacted] | [redacted] | [redacted] |
| **Scenario 2: Independently fitted OS and PFS curves for Regorafenib (Using CORRECT study data)[18]** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.529 | [redacted] | 0.108 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 3: ToT for Regorafenib: Apply ratio of mean ToT from CORRECT study / Mean modelled PFS (67.6% of progression-free patients remaining on Regorafenib treatment when applied to company base case)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 4: Apply pooled HSUVs** | | | | | | | |
| BSC | [redacted] | 0.435 | | | | | |
| FTD/TPI | [redacted] | 0.637 | [redacted] | 0.202 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.576 | [redacted] | -0.061 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.914 | [redacted] | 0.277 | [redacted] | [redacted] | [redacted] |
| **Scenario 5: Apply EAG preferred relative dose intensity for regorafenib (CORRECT study)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 6: Apply additional monitoring costs for Regorafenib (Weekly for chemo cycle 1; bi-weekly for chemo cycle 2 and monthly thereafter)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 7: Apply additional BSC costs (£13.94 per cycle)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | -0.059 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.324 | [redacted] | [redacted] | [redacted] |
| **Scenario 8: Apply eMIT costs for calcium folinate post progression treatment** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | -0.059 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.324 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 9: Apply EAG preferred post progression costs (58.3% receive treatment; distribution: regorafenib post trifluridine-tipiracil + bevacizumab & trifluridine-tipiracil alone; trifluridine-tipiracil post regorafenib)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 10: EAG preferred base case analysis (Scenarios 1-9 combined) - Deterministic** | | | | | | | |
| BSC | [redacted] | 0.431 | | | | | |
| FTD/TPI | [redacted] | 0.609 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.546 | [redacted] | -0.063 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.788 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-9 combined) - Probabilistic** | | | | | | | |
| BSC | [redacted] | 0.435 | | | | | |
| FTD/TPI | [redacted] | 0.627 | [redacted] | 0.191 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.559 | [redacted] | -0.067 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.800 | [redacted] | 0.173 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

# 2 INTRODUCTION AND BACKGROUND

## *2.1 Introduction*

The relevant health condition for the submission received from Servier is metastatic colorectal cancer after two systemic treatments. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is trifluridine-tipiracil (Lonsurf ®) plus bevacizumab (Avastin ®, or a biosimilar).

## *2.2 Background*

The company's submission (CS) describes colorectal cancer (CRC) as involving either the colon (72% of cases) or the rectum (28% of cases), although the two cancers are regarded as a single tumour entity.[1, 2] The colon is sub-divided into the right colon (the cecum, ascending colon, liver flexure, transverse colon) and left colon (splenic flexure, descending colon, sigmoid colon) and colon cancer can arise in either side.[3] Most CRC evolves over a number of years from benign neoplasms (tubular adenomas and serrated polyps).[4] Apart from those with a genetic predisposition, most polyps are found in people over 50 years of age, with some going on to develop into CRC.[5-7] Almost all CRC are adenocarcinomas, which arise in the cells that generate mucous for lubrication of the colon and rectum.[8] Early CRC can be asymptomatic, which together with developing over time from polyps forms the basis of national screening programmes. Symptoms of left-sided CRC include blood in the stool, changes in bowel habit, and, in right-sided CRC, fatigue, low-grade fever and abdominal pain.[2]

Risk factors for CRC include personal or family history of CRC, personal history of colon polyps, inflammatory bowel disease, diabetes or cholecystectomy. In addition, lifestyle factors can influence CRC aetiology, for example, overweight/obesity, physical inactivity, smoking, alcohol intake and dietary considerations (eating processed meat and/or too little fibre).[9]

On average, there are 42,886 new cases of CRC each year in the UK, accounting for 11% of all cancer diagnoses. The peak age of patients in the UK with a new diagnosis of CRC is 85-89 years with around one-third arising in the rectum. In the year 2022-2023 in England, there were 100,163 admissions and 110,393 finished consultant episodes (FCE) for malignant

neoplasm of the colon (code C18), and 49,879 admissions and 53,315 FCE for malignant neoplasm of the rectum (code C20).[10]

CRC is classified into stages according to the amount of cancer in the body, with the earliest CRC referred to as stage 0 and stages I to IV referring to increasing spread of the disease. Stage IV itself refers to metastatic CRC (mCRC), indicating spread out with the colon or rectum.[11] Common sites of metastases in CRC included liver, lung, lymph nodes and peritoneum,[12] with pelvis mainly due to those with a primary site in the rectum.[13] Prognosis is mainly associated with the stage and biomarker profile, and, in most people, mCRC is incurable.[13, 14] However, a minority can be cured by of their disease. Treatment of mCRC depends on not only the extent of the disease but also the biomarker profile of the cancer as well as the overall fitness of the patient and any co-morbidities. The aim of treatment is to improve or maintain quality of life and extend survival through control of the underlying CRC. Treatment can involve a number of modalities, including surgery (less common), radiotherapy, and systemic therapy. Best supportive care, a broad term covering a variety of approaches, may be the only option for many frail patients with significant co-morbidities, or those with such advanced disease that active treatment is inappropriate.

The current treatment pathway for mCRC in England is presented in Figure 5, Document B of the CS and reproduced in Figure 1 below.

The EAG's clinical expert agrees that the current standard of care in the 3rd-line setting is trifluridine-tipiracil and only recently has regorafenib become a funded and approved option in the UK. The EAG's clinical expert further notes that no patients with CRC and having a V600E BRAF mutation that was microsatellite stable would receive encorafenib and cetuximab in the third-line setting. In addition, it is agreed that defining 3rd-line treatment can be difficult, due to retreatment with previous chemotherapy agents, which some oncologists would count as a separate line of treatment and others would not.

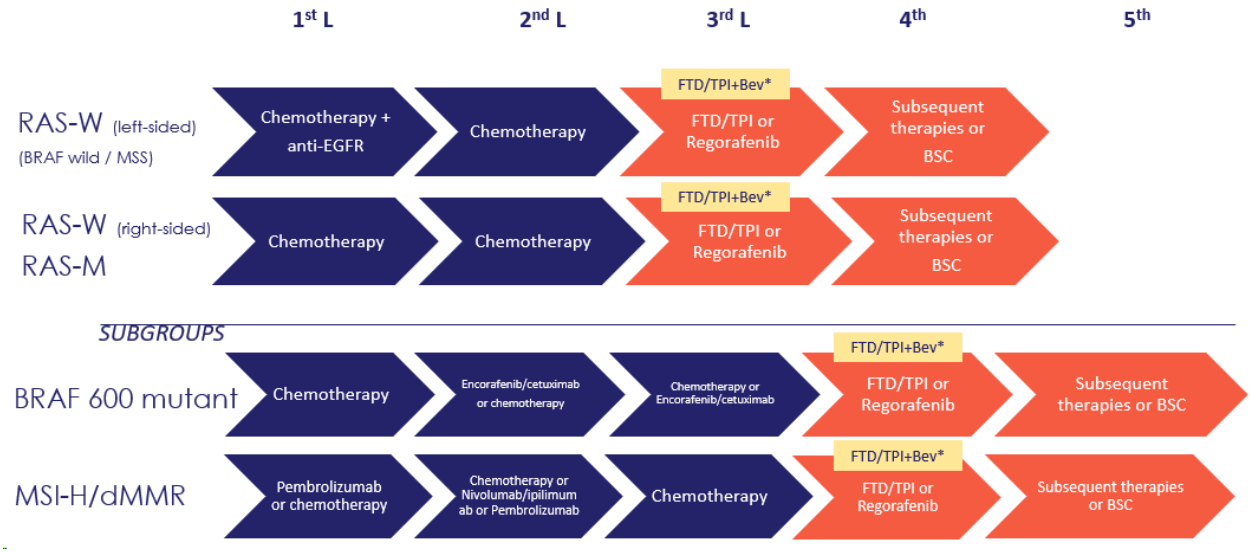



Figure adapted from NICE guidance and feedback of mCRC Therapy Area Experts.
Chemotherapy can be FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5-FU, oxaliplatin/ irinotecan).
**Key:** BSC, Best Supportive Care; FTD/TPI+Bev, trifluridine/tipiracil + bevacizumab

**Figure 1 UK mCRC schematic treatment management [reproduced from Figure 5, Document B of the CS]**

### *2.3 Critique of the company's definition of decision problem*

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

**Table 3 Summary of the company's decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| **Population** | Adults with metastatic colorectal cancer after 2 systemic treatments | Adults with metastatic colorectal cancer after 2 systemic treatments | N/A | The EAG is satisfied with the company's approach |
| **Intervention** | Trifluridine–tipiracil with bevacizumab | Trifluridine–tipiracil with bevacizumab | N/A | The EAG is satisfied with the company's approach |
| **Comparator(s)** | • Single-agent irinotecan (after FOLFOX)<br>• FOLFIRI (after either FOLFOX or CAPOX)<br>• FOLFOX (after either FOLFIRI or CAPOX)<br>• Raltitrexed (if 5-FU/FA are not suitable)<br>• Trifluridine–tipiracil monotherapy • Regorafenib<br>• Nivolumab with ipilimumab (where high microsatellite instability or mismatch repair deficiency is present)<br>• Encorafenib with cetuximab (if BRAF V600E mutation-positive metastatic colorectal cancer) | Servier considers the following comparators to be appropriate:<br>• Trifluridine–tipiracil monotherapy<br>• Regorafenib<br>• Best Supportive care | Servier do not consider all comparators listed in the scope to be appropriate.<br>• Single-agent irinotecan (after FOLFOX)<br>• Raltitrexed (if 5-FU/FA are not suitable)<br>In technology appraisal TA914 with pembrolizumab, the company stated that irinotecan and raltitrexed were excluded based on clinical feedback that they are rarely used in practice unless other treatments are contraindicated. The clinical expert and Cancer Drugs Fund lead both confirmed that irinotecan and raltitrexed monotherapy are rarely used in clinical practice. | The EAG's clinical expert considers that the comparators addressed in the CS are appropriate and agrees with the company's justification for excluding the remaining comparators |

| | | | | |
|---|---|---|---|---|
| | • Best supportive care | | • FOLFIRI (after either FOLFOX or CAPOX)<br>• FOLFOX (after either FOLFIRI or CAPOX)<br>These are second-line settings so should not be used as a comparator to Trifluridine/tipiracil + bevacizumab as the SmPC states for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have received two prior anti-cancer treatment regimens. Both the inclusion criteria of SUNLIGHT and the SPC (mentions; including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.<br>• Nivolumab with ipilimumab (where high microsatellite instability or mismatch repair deficiency is present)<br>Technology appraisal TA914 with pembrolizumab states that 4-8% of patients with | |

| | | | | |
|---|---|---|---|---|
| | | | colorectal cancer have MSI-H tumours. CHECKMATE 142 publication, references "patients with DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) mCRC to ≈4% to 5% of patients." However, only around 35 people per year are expected to have nivolumab with ipilimumab for colorectal cancer with high MSI or MMR deficiency. This number is small because pembrolizumab is already available as a first-line therapy and people can only have a checkpoint inhibitor at one point in the treatment pathway.<br>In an advisory board carried out by Servier Laboratories in July 2023 and clinical insight meetings, it was found that clinicians would use nivolumab with ipilimumab in the second line setting before trifluridine-tipiracil + bevacizumab, and, therefore, earlier in the treatment pathway. | |

| | | | | |
|---|---|---|---|---|
| | | | This regimen is used if genetic testing indicates high microsatellite instability or mismatch repair deficiency. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens.<br><br>• Encorafenib with cetuximab<br>An advisory board carried out by Servier Laboratories in July 2023 and clinical insight meetings found that clinicians would use encorafenib with cetuximab in the second line setting prior to the use of trifluridine-tipiracil + bevacizumab, and therefore earlier in the treatment pathway.<br>This regimen is used if genetic testing indicates BRAF V600E mutation positive. If | |

| | | | | |
|---|---|---|---|---|
| | | | genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine-tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens. | |
| **Outcomes** | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life | The outcome measures to be considered include:<br>• overall survival<br>• progression-free survival<br>• response rates<br>• adverse effects of treatment<br>• health-related quality of life | N/A | The EAG's clinical expert is satisfied that the outcomes addressed in the CS are appropriate to the decision problem |
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to | As per the final scope | N/A | The EAG is satisfied that the economic analysis aligns closely with the NICE reference case. Results are reported as incremental cost per QALY gained using a fully incremental and pairwise analyses, exploring a range of severity weightings. The time horizon of 15 years is |

| | | | | |
|---|---|---|---|---|
| | reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. | | | sufficiently long to reflect a lifetime horizon for a patient group that have a high mortality risk at the end of the treatment pathway. Costing perspective is appropriate and confidential arrangements for the company's products are accounted for. Confidential arrangements for bevacizumab, comparators and subsequent treatments are provided in a confidential appendix to the EAG report. |
| **Subgroups** | If the evidence allows the following subgroups will be considered. These include:<br>• People without prior bevacizumab | As per the final scope | N/A | The company performed subgroup analyses on the treatment effect on OS by 15 pre-specified subgroups, including prior bevacizumab use |
| **Special considerations including issues related to equity or equality** | None | None | N/A | N/A |

**Key:** 5-FU, fluorouracil; CAPOX, capecitabine, oxaliplatin; dMMR, DNA mismatch repair deficient; EMA, European Medicines Agency; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX; fluorouracil, leucovorin, and oxaliplatin; mCRC: metastatic colorectal cancer; MMR, mismatch repair; MSI-H, microsatellite instability-high; SmPC, summary of product characteristics

# 3 CLINICAL EFFECTIVENESS

## *3.1 Critique of the methods of review(s)*

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Document B, Section B.2.1 and Appendix D of the CS. At clarification, the company confirmed that the review reported in Appendix D referred to an update that had not been incorporated into the submission. The EAG's critique of the methods used in the review is, therefore, based on the content of Appendix D and is summarised in Table 4.

**Table 4 EAG's appraisal of the systematic review methods presented in the CS.**

| Review process EAG | EAG response | Comments |
|---|---|---|
| Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies? | YES | The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1 of the CS. |
| Were appropriate bibliographic databases/sources searched? | YES | Sources included Embase, Medline, and CENTRAL for primary research, DARE and CDSR for evidence syntheses. Relevant conference proceedings and trial registers were also searched. Full details are provided in Appendix D.1.1 of the CS. |
| Were eligibility criteria consistent with the decision problem outlined in the NICE final scope? | YES | Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected. |
| Was study selection conducted by two or more reviewers independently? | YES | Appendix D, section 3.1.3: "*During both screening stages,* |

| | | |
|---|---|---|
| | | *each publication was assessed by two independent reviewers*". |
| Was data extraction conducted by two or more reviewers independently? | PARTLY | Appendix D, section 3.1.3: "*For RCTs, data were extracted by two reviewers. For non-randomised and single-arm trials, data were extracted by a single reviewer and independently validated by a second reviewer*". The EAG is satisfied with the company's approach |
| Were appropriate criteria used to assess the risk of bias of identified studies? | YES | The Cochrane risk of bias tool version 2 was used to assess the risk of bias in included RCTs. Non-randomised and single-arm trials were assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort studies. The EAG considers the company's approach to risk of bias assessment to be appropriate |
| Was the risk of bias assessment conducted by two or more reviewers independently? | PARTLY | Appendix D, section 3.1.5: "*Risk of bias in included RCTs was assessed by two independent reviewers…*" and "*Quality assessment of non-randomised and single-arm trials was performed by a single reviewer and independently validated by a second reviewer…*". The EAG considers this to be acceptable |
| Was identified evidence synthesised using appropriate methods? | YES | The company carried out an indirect treatment comparison via a network meta-analysis, Relevant studies identified through a systematic search of the literature were included in the network meta-analysis. Fixed and random effects analyses were both carried out and presented as hazard ratios for OS and PFS assuming proportional hazards. The EAG considers the company's approach to be appropriate. |

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5. The EAG considers the methods used by the company for the systematic review of clinical effectiveness evidence to be appropriate.

**Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence**

| CRD quality item | Yes/No/Unclear |
|---|---|
| 1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question? | Yes |
| 2. Is there evidence of a substantial effort to search for all of the relevant research? | Yes |
| 3. Is the validity of included studies adequately assessed? | Yes |
| 4. Are sufficient details of the individual studies presented? | Yes |
| 5. Are the primary studies summarised appropriately? | Yes |

## *3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

### 3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, section B.2.3 of the CS. The main clinical evidence for the clinical effectiveness and safety of trifluridine-tipiracil and bevacizumab consisted of one open-label, multinational, randomised, controlled, phase III trial, SUNLIGHT. The EAG has no major concerns about the design or conduct of this trial.

The primary objective of SUNLIGHT was to demonstrate the superiority of trifluridine-tipiracil and bevacizumab over trifluridine-tipiracil monotherapy in patients with refractory metastatic colorectal cancer (mCRC) following two chemotherapy regimens. The primary endpoint was overall survival (OS). Key inclusion and exclusion criteria for SUNLIGHT are reported in Document B, Table 5 of the CS. Patients were randomised 1:1 to receive either trifluridine-tipiracil plus

bevacizumab or trifluridine-tipiracil monotherapy, in 28-day treatment cycles. The CS notes that further anti-cancer therapy could be administered during the trial, treatment could be discontinued, or treatment could be switched between arms. A summary of the trial methodology of SUNLIGHT is presented in Document B, Table 7 of the CS and reproduced in Table 6 below.

**Table 6 Summary of SUNLIGHT methodology [reproduced from Table 7, Document B of the CS]**

| | |
|---|---|
| **Study** | SUNLIGHT |
| **Study design** | open-label, multinational, randomised, controlled two-arm phase III trial |
| **Population** | 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 |
| **Intervention(s)** | Trifluridine-tipiracil + bevacizumab |
| **Comparator(s)** | Trifluridine tipiracil monotherapy |
| **Indicate if the study supports application for marketing authorisation** | Yes |
| **Indicate if study used in the economic model** | Yes |
| **Rationale if study not used in the model** | N/A |
| **Reported outcomes specified in the decision problem** | OS: Observed time elapsed between the date of randomisation and the date of death due to any cause<br>PFS: Time elapsed between randomisation and the date of radiologic tumour progression according to RECIST v1.1 by investigator's judgement or death from any cause |
| **All other reported outcomes** | ORR: Proportion of patients with objective evidence of CR or PR according to RECIST v1.1 and using investigator's tumour assessment |
| | DCR: Proportion of patients with objective evidence of CR or PR or stable disease according to RECIST v1.1 and using investigator's tumour assessment |
| | TEAEs: Assessed by CTCAE v5.0, including SAEs |
| | QoL: Assess patients' health and activities using EORTC QLQ-C30 |
| | QoL: Assess patients' health and activities using EQ-5D-5L |

**Key**: CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; EORTC QLQ-C30, European Organisation for the Research and Treatment of

Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 Dimension-5 levels; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SAEs, serious adverse events; TEAEs, treatment-related emergent adverse events

SUNLIGHT was conducted at 87 sites in 13 countries (Spain, Russian Federation, Brazil, Hungary, Italy, Poland, France, Ukraine, Denmark, USA, Austria, Germany and Belgium and was funded by Servier (outside the USA) and Taiho Oncology (in the USA). Participant flow is presented in Document B, Figure 7 of the CS. A total of 492 participants were randomised in SUNLIGHT between November 2020 and February 2022, 246 in each group. All randomised participants received the study treatment to which they were randomised. In the trifluridine-tipiracil plus bevacizumab group, 214/246 (87.0%) participants discontinued treatment, and 32/246 (13.0%) were still on treatment at the clinical data cut-off (5th July 2022). In the trifluridine-tipiracil monotherapy group, 242/246 (98.4%) discontinued treatment and 4/246 (1.6%) continued treatment. Discontinuations during the follow-up period were explained largely by deaths, specifically, 142 and 169 participants, respectively.

The company performed a quality appraisal of SUNLIGHT using Version 2 of the Cochrane Risk of Bias tool.[15] Overall, the EAG agrees with the company's assessment that SUNLIGHT was at low risk of bias, despite the fact it was an open-label trial and funded by the pharmaceutical industry.

Details of the baseline demographic and disease characteristics of SUNLIGHT are reported in Table 8, Section B.2.3.4 of the CS, reproduced as Table 7 below.

**Table 7 Baseline characteristics for patients in the SUNLIGHT phase III trial [reproduced from Table 7, Document B of the CS]**

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| ***Demographics*** | | |
| Gender, n (%) | | |
| Male | 122 (49.6) | 134 (54.5) |
| Female | 124 (50.4) | 112 (45.5) |
| Age, median years (range) | 62 (20; 84) | 64 (24; 90) |

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| <65, n (%) | 146 (59.3) | 129 (52.4) |
| ≥65, n (%) | 100 (40.7) | 117 (47.6) |
| Geographic Region, n (%) | | |
| North America | 8 (3.3) | 8 (3.3) |
| European Union | 158 (64.2) | 157 (63.8) |
| Rest of the World | 80 (32.5) | 81 (32.9) |
| ***ECOG PS, n (%)*** | | |
| 0 | 119 (48.4) | 106 (43.1) |
| 1 | 127 (51.6) | 139 (56.5) |
| 2 | 0 | 1 (0.41)[a] |
| ***Primary site, n (%)*** | | |
| Colon | 180 (73.2) | 181 (73.6) |
| Rectum | 66 (26.8) | 65 (26.4) |
| ***Primary tumour location, n (%)*** | | |
| Right | 62 (25.2) | 77 (31.3) |
| Left | 184 (74.8) | 169 (68.7) |
| ***Number of metastatic organ sites, n (%)*** | | |
| 1-2 | 152 (61.8) | 141 (57.3) |
| ≥3 | 94 (38.2) | 105 (42.7) |
| ***Previous metastatic drug treatment, n (%)*** | | |
| Fluoropyrimidine | 246 (100) | 246 (100) |
| Irinotecan | 246 (100) | 245 (99.6) |
| Oxaliplatin | 241 (98.0) | 243 (98.8) |
| Anti-VEGF | 178 (72.4) | 176 (71.5) |
| Anti-EGFR in *RAS* WT* | 67/71 (94.4) | 66/71 (93.0) |
| ***Number of prior metastatic drug regimens, n (%)*** | | |
| 1 | 11 (4.5) | 15 (6.1) |
| 2 | 229 (93.1) | 224 (91.1) |
| ≥ 3 | 6 (2.4) | 7 (2.8) |
| ***Tumour mutational status, n (%)*** | | |
| *RAS* | | |
| Mutant | 171 (69.5) | 170 (69.1) |
| WT | 75 (30.5) | 76 (30.9) |
| *BRAF* | | |
| Mutant | 8 (3.3) | 11 (4.5) |
| WT | 159 (64.6) | 156 (63.4) |
| Unknown/Missing data | 79 (32.1) | 79 (32.1) |

| Characteristics | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| MMR/MSI | | |
| MSI/high/MMR deficient | 13 (5.3) | 8 (3.3) |
| MSS/MSI low/MMR proficient | 139 (56.5) | 145 (58.9) |
| Unknown/Missing data | 94 (38.2) | 93 (37.8) |
| ***Site of metastasis, n (%)[b]*** | | |
| Liver | 194 (78.86) | 188 (76.42) |
| Lung | 157 (63.82) | 154 (62.60) |
| Lymph node | 95 (38.62) | 101 (41.06) |
| Peritoneal | 60 (24.39) | 60 (24.39) |
| Soft tissue | 9 (3.66) | 9 (3.66) |
| Bone | 22 (8.94) | 30 (12.20) |
| Brain | 2 (0.81) | 0 |
| Skin | 0 | 1 (0.41) |
| Other | 31 (12.60) | 38 (15.45) |
| ***Prior treatment with bevacizumab, n (%)[b]*** | | |
| No | 68 (27.64) | 70 (28.46) |
| Yes | 178 (72.36) | 176 (71.54) |

**Source**: Prager 2023[16]

**Note**: Data was used until 19 July 2022. Percentages are based on N, except (*) based on the number of patients for whom RAS Status was wild-type. [a]One patient had an ECOG PS rated 2 at baseline prior to treatment while it was rated 1 at inclusion; [b]data from CSR.

**Key**: CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable; N/A, not applicable; PS, performance status; SD, standard deviation; VEGF, vascular endothelial growth factor; WT, wild-type.

In general, the baseline demographic characteristics were similar between the groups. There were more males (54.5%) than females (45.5%) in the trifluridine-tipiracil monotherapy group but there were similar proportions in the intervention group (49.6% and 50.4%, respectively). Both groups included more people under 65 years of age (59.3% in the intervention group, and 52.4% in the comparator group) than over 65s (40.7% and 47.6%, respectively). There was a larger proportion of participants with colon cancer (73.2% and 73.6%) than with rectal cancer (26.8% and 26.4%) in both groups and left-sided primary tumours (74.8% and 68.7%) were more common than the right side. Nearly three-quarters of participants in both groups had prior treatment with bevacizumab. The company acknowledges that patients in the

UK would not receive bevacizumab, and this was confirmed by the EAG's clinical expert.

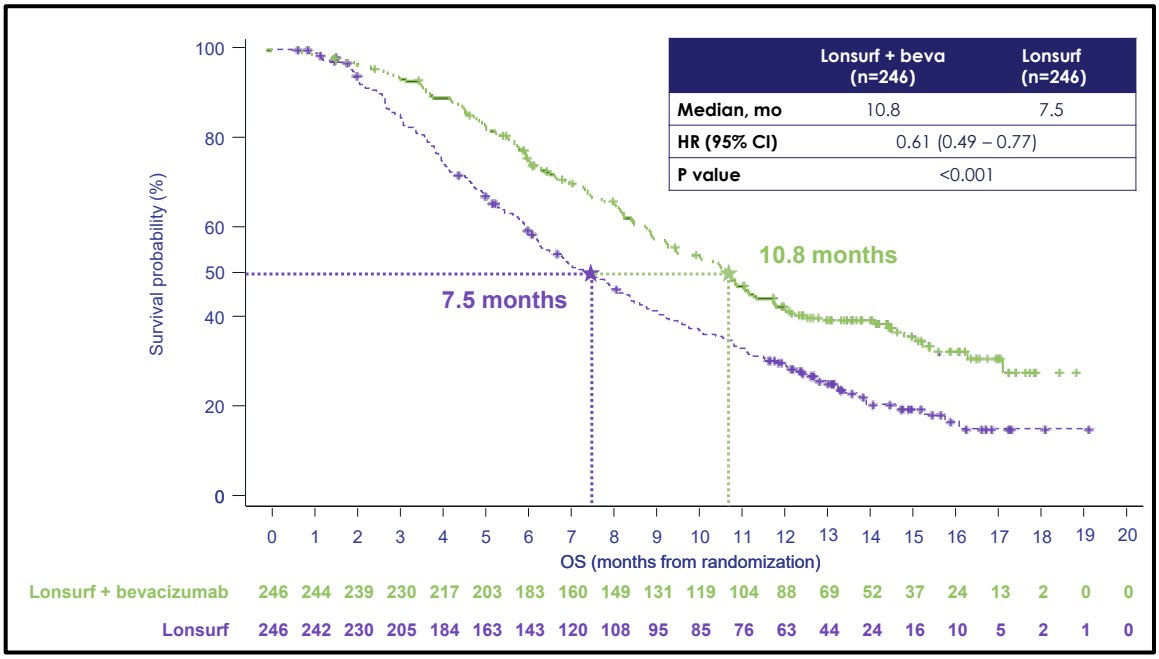
The CS states that participants' characteristics at baseline were balanced between the groups and were representative of the target population. The EAG's clinical expert notes that the median age of patients with mCRC seen in clinical practice in the UK would be older than 62 years and their ECOG PS would generally be 1 with some tending towards 2 and very few at 0. In other words, the patients in SUNLIGHT were generally younger and fitter than those who would be eligible for this treatment in the UK.

### 3.2.2 Primary and secondary efficacy endpoints

The outcomes listed in the NICE final scope for this appraisal were: overall survival (OS), progression-free survival (PFS), response rates, adverse events, and health-related quality of life (HRQoL). The full analysis set for efficacy outcomes consisted of all patients who were randomised, and patients were analysed in the arm to which they were randomised.

*Primary endpoint: overall survival (OS)*

The primary endpoint of SUNLIGHT was OS, defined as the observed time between date of randomisation and date of death due to any cause. At the time of the primary analysis (19-07-2022), 148/246 (60.2%) of the trifluridine-tipiracil plus bevacizumab group and 183/246 (74.4%) of the trifluridine-tipiracil monotherapy group had died. Median (IQR) follow-up was 14.2 months (12.6, 16.4) in the trifluridine-tipiracil plus bevacizumab group and 13.6 months (12.7, 15.9) in the trifluridine-tipiracil monotherapy group. The company presents a Kaplan-Meier plot for OS in Figure 8, Document B of the CS, reproduced as Figure 2 below. Median (95%CI) OS in the trifluridine-tipiracil plus bevacizumab group was 10.8 months (9.4, 11.8) as compared to 7.5 months (6.3, 8.6) in the trifluridine-tipiracil monotherapy group (HR 0.61 95%CI 0.49, 0.77, $p<0.001$). Survival probability (95%CI) at 6 months was 77% (72, 82) and 61% (55, 67), respectively; at 12 months: 43% (36, 49) and 30% (24%, 36%), respectively; and at 18 months: 28% (19, 37) and 15% (9, 22), respectively.




**Source**: Prager 2023[16]; **Notes:** Primary analysis of OS was performed on survival data on 19 July 2022, using FAS of 492 patients with mCRC; **Key**: 3L, third-line; beva, bevacizumab; CI, confidence interval FAS, full analysis set; HR, hazard ratio; Lonsurf; trifluridine-tipiracil; mCRC, metastatic colorectal cancer; mo, months; OS, overall survival

**Figure 2 Kaplan-Meier curve for OS in patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS]) [reproduced from Figure 8, Document B of the CS]**

*Secondary endpoints*

- **Progression-free survival** (PFS; time lapsed between randomisation and date of radiologic tumour progression according to RECIST v1.1 by investigator's judgement or death from any cause): Median (95%CI) PFS in the trifluridine-tipiracil plus bevacizumab group was 5.6 months (4.5, 5.9) and 2.4 months (2.1, 3.2) in the trifluridine-tipiracil monotherapy group (HR 0.44, 95%CI 0.36, 0.54, p<0.001). The company presents a Kaplan-Meier plot for PFS in Figure 9, Document B of the CS. The probability of being progression-free was consistently higher in the trifluridine-tipiracil plus bevacizumab group than in the monotherapy group at 3 (73% vs 45%), 6 (43% vs 16%), 9 (28% vs 5%) and 12 months (16% vs 1%).

- **Overall response rate** (ORR; proportion of patients with objective evidence of complete response [CR] or partial response [PR] according to RECIST v1.1 and using investigator's tumour assessment): ORR was 6.1% in the trifluridine-tipiracil plus bevacizumab group and 1.2% in the monotherapy group (between-group difference 4.9%; 95%CI 1.6, 8.2; p=0.007). A summary of tumour response is presented in Table 13, Document B of the CS and reproduced in Table 8 below.

**Table 8 Summary of tumour response for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, n=492 [FAS]) [reproduced from Table 13, Document B of the CS]**

| Tumour Response | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil (n=246) |
|---|---|---|
| CR, n (%) | 0 (-) | 1 (0.4) |
| PR, n (%) | 15 (6.1) | 2 (0.81) |
| Stable disease, n (%) | 156 (63.41) | 100 (40.65) |
| ORR, n (%) | 15 (6.10) | 3 (1.22) |
| DCR, n (%) | 171 (69.51) | 103 (41.87) |

**Source**: Prager 2023[16]; SUNLIGHT Clinical Study Report page 82[17]

**Note**: Responses recorded after intercurrent event (e.g. additional anti-cancer treatment or treatment arm switch) were excluded to align with the "while on treatment" strategy

**Key**: 3L, third line; CR, complete response; CSR, clinical study report; DCR, disease control rate; FAS, full analysis set; mCRC, metastatic colorectal cancer; ORR, overall response rate; PR, partial response

The between-group difference for DCR was 27.6 (95%CI 19.2, 36.1; p<0.001).

- **Health-related quality of life** (HRQoL): HRQoL was assessed using the EORTC QLQ-C30 and EuroQol EQ-5D-5L questionnaires. The company states that patients in both treatment groups maintained cancer related and general HRQoL from baseline to Cycle 6 and did not report increased symptom burden over time. Median time to definitive deterioration in EORTC QLQ-C30 global health status was 8.5 months in the trifluridine-tipiracil plus

bevacizumab group and 4.7 months in the monotherapy group (HR 0.50; 95%CI 0.38, 0.65; p<0.001).

### 3.2.3 Subgroup analyses

To assess the homogeneity of treatment effect across patient subgroups, the company performed subgroup analyses of OS for 15 pre-specified subgroups (reported in Section B.2.7, Document B of the CS). For all subgroups, HRs were observed to be in favour of trifluridine-tipiracil plus bevacizumab and the effect was significant regardless of previous exposure to bevacizumab.

*The EAG agrees that overall, the subgroup analyses demonstrated the superiority of trifluridine-tipiracil plus bevacizumab over trifluridine-tipiracil monotherapy for most subgroups. The EAG notes that while the effect advantage of trifluridine-tipiracil plus bevacizumab over trifluridine-tipiracil monotherapy was maintained regardless of prior bevacizumab use, patients without prior exposure seemed to have better response (lower hazards) than those with previous exposure.*

### 3.2.4 Adverse events

The safety set in SUNLIGHT was defined as all patients who took at least one dose of trifluridine-tipiracil, with patients analysed according to the treatment they received. At the cut-off date of 5th July 2022, the mean (SD) treatment duration was 6.1 (4.3) months for the trifluridine-tipiracil plus bevacizumab group and 3.4 (2.5) months for the monotherapy group. An overall safety summary is provided by the company in Table 27, Document B of the CS, reproduced as Table 9 below.

The EAG noted inconsistencies in the reporting of adverse events between the CS and the SUNLIGHT CSR, in particular, relating to those reported as “treatment-related emergent adverse events” (interpreted by the EAG as TEAEs) in the CSR being reported as TEAEs in the CS. For the following section, the main source of evidence was the CSR.

**Table 9 Overall safety summary for patients with mCRC receiving trifluridine-tipiracil + bevacizumab or trifluridine-tipiracil monotherapy as 3L treatment (SUNLIGHT trial, N= 492 [SS]) [reproduced from Table 27, Document B of the CS]**

| Event (any cause), n (%) | Trifluridine-tipiracil + bevacizumab (n=246) | Trifluridine-tipiracil monotherapy (n=246) |
|---|---|---|
| Overall AE | 241 (98.0) | 241 (98) |
| Severe (Grade ≥3) AE | 178 (72.4) | 171 (69.5) |
| Serious AE | 61 (24.8) | 77 (31.3) |
| AE leading to trifluridine-tipiracil withdrawal | 31 (12.6) | 31 (12.6) |
| Dose reductions | 40 (16.3) | 31 (12.2) |
| Dose delays | 171 (69.5) | 131 (53.3) |

**Source**: Prager 2023[16]; SUNLIGHT Clinical Study Report table (13.3) 1[17]

**Key:** 3L, third line; AE, adverse event; CSR, clinical study report; mCRC, metastatic colorectal cancer; SS, safety set

Most participants (98%) in both groups experienced at least one AE with around three-quarters experiencing AEs of at least Grade 3. A greater proportion of participants in the monotherapy group (31.3%) experienced serious AEs than those in the combination group (24.8%). Table 10 presents a summary of treatment-emergent AEs occurring in at least 20% of either treatment group.

**Table 10 Treatment-emergent AEs reported in ≥20% of either treatment group (adapted from Table 2, Prager 2023[16] and Table (12.2.2)2 of the SUNLIGHT CSR)[17]**

| Event, n (%) | Trifluridine-tipiracil + bevacizumab (n=246) | | Trifluridine-tipiracil monotherapy (n=246) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| Neutropenia | 153 (62.2) | 106 (43.1) | 126 (51.2) | 79 (32.1) |
| Nausea | 91 (37.0) | 4 (1.6) | 67 (27.2) | 4 (1.6) |
| Anaemia | 71 (28.9) | 15 (6.1) | 78 (31.7) | 27 (11.0) |
| Asthenia | 60 (24.4) | 10 (4.1) | 55 (22.4) | 10 (4.1) |
| Fatigue | 53 (21.5) | 3 (1.2) | 40 (16.3) | 9 (3.7) |
| Diarrhoea | 51 (20.7) | 2 (0.8) | 46 (18.7) | 6 (2.4) |
| Decreased appetite | 50 (20.3) | 2 (0.8) | 38 (15.4) | 3 (1.2) |

According to the CSR (page 96 and Table (13.3)1), treatment-emergent AEs leading to death during the treatment period or follow-up were lower in the trifluridine-tipiracil plus bevacizumab group (5.3%) than in the monotherapy group (11.0%). The CS (Table 30, Document B) reports no TEAEs leading to death in either group. It is believed by the EAG that this figure refers to treatment-related TEAEs leading to death (as reported in Table (13.3)1 of the CSR).

Treatment-related AEs were experienced by 90.7% of participants in the trifluridine-tipiracil plus bevacizumab group and 81.3% of the monotherapy group, as reported by the CSR. Of these, 89.8% and 81.3%, respectively, were attributed to trifluridine-tipiracil and 48.4% of the trifluridine-tipiracil plus bevacizumab group had events related to bevacizumab. Severe treatment-related TEAEs were reported in 58.9% of the trifluridine-tipiracil plus bevacizumab group and 45.5% of the monotherapy group. Serious treatment-related TEAEs were reported in 5.3% and 8.1%, respectively. There were no treatment-related deaths.

*Overall, the EAG's clinical expert is satisfied that the range and grade of adverse events reported in the CS are as expected from clinical use of trifluridine-tipiracil and bevacizumab in patients in the 3$^{rd}$-line setting and has no concerns*.

### *3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison.*

As SUNLIGHT provides evidence only for the comparison of trifluridine-tipiracil and bevacizumab versus trifluridine-tipiracil monotherapy, the company conducted an NMA to compare trifluridine-tipiracil and bevacizumab with regorafenib and BSC. Evidence for the NMA came from 15 connected RCTs out of twenty-six RCTs identified by the company's SLR. The company submission presents information and results of seven of these RCTs (five phase III trials and two phase II trials, with different blinding schedules), which assess comparators relevant to the UK clinical practice and the decision problem of this appraisal. Two trials included three treatment arms while the remaining trials included two treatment arms. Table 20 of Document B in the company submission shows the number of prior lines of therapy received by the participants enrolled in these trials. The EAG notes that most of these studies were conducted in a broader population with many participants having

received 3 or more prior lines of therapy. This is in contrast with the NICE final scope that stipulated a population of adults with metastatic colorectal cancer after 2 systemic treatments. Nevertheless, the EAG's clinical expert maintains that this is not expected to have a significant impact on the fitness of the participants, as compared to those in the SUNLIGHT trial who had undergone 2 or fewer prior therapies. Table 21 of Document B of the company submission summarises the proportion of patients who received prior bevacizumab-containing regimens. The EAG notes that for two trials the percentage of patients who received bevacizumab was not reported. Additionally, in one trial, namely TERRA, the proportion of patients who received bevacizumab is considerably lower than in other trials. However, the EAG's clinical expert believes that this disparity is unlikely to cause any additional uncertainty in the findings. All the trials have used a similar definition of outcomes. The company has performed a post-hoc analysis to investigate if the prior regimen is an effect modifier for trifluridine-tipiracil versus placebo. The company used three methods to investigate the treatment effect by the number of prior regimens on the data from the RECOURSE study: (a) interaction term analysis in a univariate model (b) interaction term analysis in a multivariate model (c) stratification analysis in a multivariate model. In all three models, p values for the number of prior regimens were statistically not significant indicating that there is no evidence that the line of treatment modifies the treatment effects (Appendix P). *The EAG agrees that there is no evidence of treatment effect modification.* Table 11 below shows a summary of OS and PFS results from the seven trials included in the NMA.

**Table 11 Summary of OS and PFS outcomes of trials included in NMA - investigator-assessed [adapted from Tables D9 and D10, Appendix D of the CS]**

| Study ID | Arm | N | OS, median months (95%CI) | PFS, median months (95%CI) |
|---|---|---|---|---|
| CONCUR | Regorafenib | 68 | 6.3 (4.8, 7.6) | 1.7 (1.6, 1.8) |
| | Placebo | 136 | 8.8 (7.3, 9.8) | 3.2 (2, 3.7) |
| CORRECT | Regorafenib | 505 | 6.4 (IQR 3.6, 11.8) | 1.9 (IQR 1.6, 3.9) |
| | Placebo | 255 | 5 (IQR 2.8, 10.4) | 1.7 (IQR 1.4, 1.9) |
| Pfeiffer 2020 | Trifluridine-tipiracil plus bevacizumab | 47 | 6.7 (4.9, 7.6) | 4.6 (3.5, 6.5) |
| | Trifluridine-tipiracil | 46 | 9.4 (7.6, 10.7) | 2.6 (1.6, 3.5) |
| RECOURSE | Trifluridine-tipiracil | 534 | 7.2 (6.6, 7.8) | 2 (1.9, 2.1) |
| | Placebo | 266 | 5.2 (4.6, 5.9) | 1.7 (1.7, 1.8) |
| SUNLIGHT | Trifluridine-tipiracil plus bevacizumab | 246 | 10.8 (9.4, 11.8) | 5.6 (4.5, 5.9) |
| | Trifluridine-tipiracil | 246 | 7.5 (6.3, 8.6) | 2.4 (2.1, 3.2) |
| TERRA | Trifluridine-tipiracil | 271 | 7.8 (7.1, 8.8) | 2 (1.9, 2.8) |
| | Placebo | 135 | 7.1 (5.9, 8.2) | 1.8 (1.7, 1.8) |
| Yoshino 2014 | Trifluridine-tipiracil | 112 | 9.0 (7.3, 11.3) | 2.7 (1.9, 3.2) |
| | Placebo | 57 | 6.6 (4.9, 8.0) | 1.0 (1.0, 1.0) |

### *3.4 Critique of the indirect comparison and/or multiple treatment comparison*

The NMA for OS included 14 trials comparing nine different treatments while the NMA for PFS included 15 trials comparing 10 different treatments. The company specifies that only trifluridine-tipiracil plus bevacizumab, trifluridine-tipiracil monotherapy, regorafenib and BSC were considered in the cost-effectiveness analyses. The company conducted NMAs using both fixed-effect and random-effects models. The trifluridine-tipiracil plus bevacizumab combination resulted in lower HR for OS and PFS against trifluridine-tipiracil, regorafenib, and BSC indicating a favourable effect for both random-effects and fixed-effect models. *The EAG agrees that evidence presented by the company demonstrates the superiority of trifluridine-tipiracil plus bevacizumab over trifluridine-tipiracil monotherapy, regorafenib and BSC for both OS and PFS.* Tables 12 and 13 show the summary of random effects and fixed effects NMA results for OS and PFS. Results from the fixed effects and random effects models were similar with the random effect models having, as expected, slightly wider credible intervals. The EAG notes that the NMA was based on reported HRs with assumed proportionality in hazards. The company acknowledges that this assumption may bias the results at "*certain timepoints and [that] extrapolations*

*should be considered with caution*." The EAG agrees with the company's statement but also considers that since OS for mCRC is less than 30% at 18 months, the long-term effects of extrapolations are unlikely to become an issue.

**Table 12 Results of random-effects and fixed effects NMA for OS based on constant HRs [adapted from Tables D10 and D11, Appendix D of the CS]**

| Random effect | | | |
|---|---|---|---|
| | **Trifluridine-tipiracil** | **Regorafenib** | **Placebo/BSC** |
| Trifluridine-tipiracil + bevacizumab | **0.59 (0.43, 0.79)** | **0.60 (0.38, 0.95)** | **0.41 (0.28, 0.58)** |
| **Fixed effect** | | | |
| Trifluridine-tipiracil + bevacizumab | **0.59 (0.49, 0.73)** | **0.59 (0.44, 0.79)** | **0.42 (0.33, 0.53)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 level.

**Table 13 Results of random-effects and fixed effects NMA for PFS based on constant HRs [adapted from Tables D12 and D13, Appendix D of the CS]**

| Random effect | | | |
|---|---|---|---|
| | **Trifluridine-tipiracil** | **Regorafenib** | **Placebo/BSC** |
| Trifluridine-tipiracil + bevacizumab | **0.46 (0.34, 0.64)** | **0.49 (0.31, 0.84)** | **0.21 (0.14, 0.31)** |
| **Fixed effect** | | | |
| Trifluridine-tipiracil + bevacizumab | **0.45 (0.38, 0.54)** | **0.46 (0.35, 0.60)** | **0.21 (0.17, 0.26)** |

**Key:** BSC, best supportive care; CrI, credible interval; HR, hazard ratio.

**Note:** Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 level.

### *3.5 Additional work on clinical effectiveness undertaken by the EAG*

No additional work has been undertaken by the EAG.

### *3.6 Conclusions of the clinical effectiveness section*

In the company's submission, the main source of evidence for the clinical effectiveness of trifluridine-tipiracil and bevacizumab in patients with metastatic colorectal cancer following two chemotherapy regimens is the SUNLIGHT phase III trial. The trial results demonstrate the superiority of trifluridine-tipiracil and bevacizumab over trifluridine-tipiracil monotherapy for the outcomes outlined in the NICE final scope. The EAG considers the treatment effects in the trial to be robust and generalisable to the clinical population of patients defined in the final scope.

The indirect comparisons (NMAs) conducted by the company to compare trifluridine-tipiracil and bevacizumab with other relevant comparators (trifluridine-tipiracil monotherapy, regorafenib, placebo/BSC), demonstrate the superiority of trifluridine-tipiracil and bevacizumab for PFS and OS. The EAG considers that the NMA results represent a robust estimation of the treatment effects. The heterogeneity noted in the number of prior lines of therapy in the trials included in the NMA would, in the view of the EAG's clinical expert, not significantly impact the fitness of participants compared with those included in the SUNLIGHT trial.

The EAG considers that the clinical evidence presented in the company's submission adequately demonstrates the effectiveness of trifluridine-tipiracil and bevacizumab over the comparators of interest.

# 4 COST EFFECTIVENESS

## *4.1 EAG comments on the company's review of cost-effectiveness evidence.*

The company conducted a systematic review of economic evaluation studies and three further supplementary reviews to identify parameters for populating the model (health-related quality of life studies and cost and health care resource identification, measurement and valuation) as reported in section B.3.1 and appendices G, H and I of their submission. Searches were conducted on the 10th of February 2023 and were restricted to studies published from the year when third line (3L) treatments for advanced and mCRC appeared in the literature (2010) to present. The SLRs identified a total of 43 reports, 35 reports were formal cost-effectiveness studies, and eight were descriptive HCRU/cost studies. Whilst one study was identified that evaluated trifluridine-tipiracil with bevacizumab as the intervention, the company did not deem it suitable to support the current economic evaluation as it was based on a different perspective (US) and there was not sufficient detail to enable the interpretation of the economic analysis. Instead, the company used previous economic models submitted to NICE within the mCRC setting to inform the model structure, assumptions, and data sources.

*The EAG notes that the company have undertaken a thorough review of the published economic evidence of relevance to this appraisal. Whilst a detailed description of review findings was not provided in the submission document, detailed tables are available in the appendices for information. The EAG agrees that the company's use of the systematic review within this assessment is appropriate.*

## *4.2 Summary and critique of the company's submitted economic evaluation by the EAG*

### 4.2.1 NICE reference case checklist

Table 14 describes the EAG's assessment of the company submission against the NICE reference case.

**Table 14 NICE reference case checklist**

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | Aligns with the reference case. Health effects were measured using life year and QALYs gained derived from OS and PFS survival curves. |
| Perspective on costs | NHS and PSS | Aligns with the reference case |
| Type of economic evaluation | Cost-utility analysis with fully incremental analysis | Aligns with the reference case.<br><br>Both pairwise and fully incremental analyses were presented. However, the EAG noted that the calculation of incremental costs and QALYs in results tables do not exclude extendedly dominated strategies. However, ICER calculations do. There is no impact on overall cost-effectiveness conclusions. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Aligns with the reference case. A 15-year time horizon is applied, and this is sufficient to capture a lifetime for the modelled patient group. Increasing the lifetime horizon further has little impact on results. |
| Synthesis of evidence on health effects | Based on a systematic review | Aligns with the reference case. The OS and PFS evidence for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy are derived from the SUNLIGHT study.[16] Regorafenib and BSC health effects are obtained from an NMA. Scenario analysis was conducted using OS and PFS survival curves for regorafenib fitted to KM data from the CORRECT study.[18] |

| Element of health technology assessment | Reference case | EAG comment on company's submission |
|---|---|---|
| | | |
| Measuring and valuing health effects | Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults. | Aligns with the reference case. QALYs calculated using EQ-5D-5L data mapped to 3L from the SUNLIGHT study.[16, 19] Treatment-dependent HSUVs derived from mixed-effects regression modelling in the company base case. EAG prefers treatment pooled HSUVs. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | Aligns with the reference case. HSUVs based on patient-reported responses to the EQ-5D-5L from the SUNLIGHT study.[16] |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | Aligns with the reference case |
| Equity considerations | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Aligns with the reference case. Severity weightings, based on QALY shortfalls are applied for this assessment and discussed further in Chapter 5.[20] |
| Evidence on resource use and costs | Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS | Aligns with the reference case, though there remains some uncertainty about the most appropriate costing assumptions, particularly for regorafenib time on treatment. |
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Aligns with the reference case |

**Key:** EQ-5D, standardised instrument for use as a measure of health outcome; PSS, personal social services; QALYs, quality-adjusted life years.

### 4.2.2 Model structure

The company submitted a *de novo* cost-effectiveness model developed in Microsoft Excel using an area-under-the-curve, partitioned survival analysis (PartSA) structure, with three

health states: progression free, progressed disease and death (See Figure 19 of document B in the company submission). Health state occupancy is determined by independently modelled progression-free survival (PFS) and overall survival (OS) curves. The progression-free proportion of the cohort was split into those on and off treatment for the application of treatment acquisition and administration costs. For trifluridine-tipiracil with bevacizumab, the proportion on treatment was considered separately for each treatment, with time to treatment discontinuation fitted independently to each treatment to allow for the possibility that patients can stop bevacizumab treatment before trifluridine-tipiracil. For regorafenib and BSC, OS and PFS were obtained from a random-effects NMA, and for regorafenib, time on treatment (ToT) was assumed equal to PFS.

*The EAG is satisfied that the company's decision to use a PartSA model structure is appropriate. Specific assumptions used to determine OS, PFS and ToT are critiqued further in Section 4.2.6.*

### 4.2.3 Population

The population considered in the cost-effectiveness analysis is adults with mCRC after two systemic treatments (Section B.3.2.1, document B of the company submission). The base case modelled population (mean starting age 62, proportion female: 48%) reflects the whole ITT population from the final analysis set in the SUNLIGHT trial.

*One difference between the SUNLIGHT clinical trial population and UK clinical practice relates to the prior use of bevacizumab. Most patients (72%) in the SUNLIGHT study had prior treatment with bevacizumab, but the corresponding proportion in UK clinical practice is likely to be closer to zero because the treatment is not routinely available to clinicians treating mCRC. Whilst there are no significant subgroup effects by prior bevacizumab treatment in the clinical effectiveness analyses, these would not be anticipated given that the trial was not powered to detect differences for this subgroup specifically. However, the EAG notes that the point estimate of the treatment effect is larger for those without, compared to those with prior bevacizumab treatment. Details of company scenario analyses, using SUNLIGHT data for the proportion of the trial cohort without prior bevacizumab treatment are presented in Appendix M of the submission for completeness. Given that most UK patients will not have received prior bevacizumab treatment, the EAG agrees that the company's approach to using the whole ITT population is conservative. It is however*

*appropriate for decision making because using the ITT population reduces bias, ensures more data are available for estimating OS and PFS parameters and thus is likely to reduce overall uncertainty in the cost-effectiveness estimates. It is also appropriate to use a conservative estimate given that, in the future, the use of bevacizumab at earlier treatment lines may increase.*

*The EAG is satisfied that the modelled population is in line with the anticipated marketing authorisation for trifluridine-tipiracil + bevacizumab, and the final scope for this appraisal issued by NICE.[21] Despite some potential overestimation of ICERs by including patients exposed to prior bevacizumab use, the EAG is satisfied that the company's approach is conservative and appropriate. The EAG's clinical expert is also of the view that the use of bevacizumab earlier in the pathway may increase over time and it is therefore prudent to use the full ITT set for analysis.*

### 4.2.4 Interventions and comparators

***Intervention***

The intervention considered within the scope of this evaluation is trifluridine-tipiracil in combination with bevacizumab. Trifluridine-tipiracil is an oral cytotoxic chemotherapy, administered at a dose of 35 mg/m2 twice daily on days 1 to 5 and 8 to 12 of each 28-day treatment cycle. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A). Bevacizumab is administered intravenously at a dose of 5 mg/kg every two weeks.

*The EAG is satisfied that the intervention dosing cost in the company's economic model is aligned with the SUNLIGHT study, the relevant marketing authorisations, and is consistent with how this treatment would likely be used in UK clinical practice.[16, 22, 23]*

***Comparators***

Although the final scope issued by NICE highlights nine potential comparators to trifluridine-tipiracil with bevacizumab, the economic model included three comparators that are reflective of available treatments in UK clinical practice: trifluridine-tipiracil monotherapy, regorafenib or best supportive care. The company indicated that this approach was aligned with the treatment pathway presented in TA866 (regorafenib for previously treated metastatic colorectal cancer)[24] and was consistent with feedback received from clinical experts who

stated that currently, they would consider either trifluridine-tipiracil, regorafenib or best supportive care in the third-line setting.

*The EAG has cross-checked the costing approach for intervention and all comparators in the model and is satisfied that the costing approach accurately reflects the dosing applied in the clinical studies, is aligned with previous NICE guidance for regorafenib and is consistent with the dosing that would be expected for these treatments in routine UK clinical practice. The EAG's clinical expert is satisfied that the company's rationale for the exclusion of several comparators from the NICE scope is appropriate and reflective of UK clinical practice.*

### 4.2.5 Perspective, time horizon and discounting

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS).[25] The cost-effectiveness analysis adopts a lifetime horizon of 15-years, which was considered long enough to adequately capture the lifetime of patients at a starting age of 62 with mCRC after two systemic treatments. The model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for patients with mCRC, being treated with trifluridine-tipiracil or a comparator. Due to the short cycle length, a half-cycle correction is not applied. As per the NICE reference case, all health effects were measured in quality-adjusted life years (QALYs) with a 3.5% discount applied to costs and QALYs.

*The EAG is satisfied with the company's modelling perspective. The EAG's clinical expert is of the view that it is highly unlikely that any patients would remain alive beyond five years in this patient population, regardless of the treatment arm, therefore a 15-year time horizon is sufficient to capture all the important differences between benefits and costs. Discounting has been applied appropriately throughout the model and is in line with the NICE reference case.*[26]

### 4.2.6 Treatment effectiveness and extrapolation

Overall survival (OS), progression-free survival (PFS) and time on treatment (ToT) for trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil alone were informed by data from the open-label, multi-national, randomised SUNLIGHT phase III trial (data cut 19 July 2022). KM data from the trial were extrapolated over a longer-term time horizon by

independently fitting survival curves (exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull) to the observed data. Further details of curve selection, including testing proportional hazards assumptions are provided in Appendix N of the company submission.

Base case efficacy parameters for the other comparators (regorafenib and BSC) were based on results from an NMA, applying hazard ratios to the fitted trifluridine-tipiracil plus bevacizumab OS and PFS curves. Regorafenib TOT was assumed to be equal to PFS. Further data and details of the NMA are provided in Appendix D of the company submission.

*The EAG is broadly satisfied that the company's methodological process for selecting parametric survival curves is appropriate for decision-making and follows best practice recommendations of the NICE Decision Support Unit (DSU) Technical Support Document number 14, such as assessment of visual and statistical fit to the observed data and clinical expert valuation of longer-term outcomes.[27] The EAG is also satisfied that fitting independent survival curves is appropriate, rather than relying on a limited number of treatment extrapolation curves on which an HR could be applied due to the requirement to meet a proportional hazards assumption. A detailed critique of the clinical effectiveness review and NMA are provided in Chapter 3. There are, however, several points of disagreement between the company and the EAG regarding the most appropriate modelling assumptions and these are detailed separately for OS, PFS and TOT in the sections that follow.*

***Overall Survival***

Trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy

For both trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy, the company reported that most parametric survival curves appear to provide a good statistical and visual fit to the observed data, except for the exponential distribution. The choice of the optimal curve amongst the candidate options was informed by clinical expert opinion sought by the company about the likely proportion of patients alive at 2 years and 5 years for each treatment arm. Six clinical experts were consulted. The clinical expert view was that for trifluridine-tipiracil monotherapy, 2-10% would be alive at 2 years, with few or no patients alive at 5 years. By contrast, they expected 15-20% alive at 2 years and 2.9% was considered a reasonable assumption at 5 years for trifluridine-tipiracil + bevacizumab. Table 15 below summarises the available data from the company submission in terms of AIC, BIC, clinical

expert expectations and modelled OS outputs at each year up to year 5 for trifluridine-tipiracil monotherapy and trifluridine-tipiracil + bevacizumab, respectively.

**Table 15 Comparison of statistical goodness of fit, company clinical expert opinion and modelled outcomes for trifluridine-tipiracil monotherapy and trifluridine-tipiracil + bevacizumab overall survival for different parametric survival curves**

| Model | Statistical fit | | OS landmarks (years) | | | | |
|---|---|---|---|---|---|---|---|
| | AIC | BIC | 1 | 2 | 3 | 4[C] | 5 |
| **Trifluridine-tipiracil monotherapy** | | | | | | | |
| Company clinical expert opinion | -- | -- | -- | 2%-10% | -- | -- | <1%[A] |
| KM data | -- | -- | 30.0% | - | - | - | - |
| Exponential | 1230.5 | 1234.0 | 32.2% | 10.4% | 3.3% | 1.1% | 0.3% |
| Generalized gamma | 1183.1 | 1193.6 | 28.6% | 8.2% | 3.1% | 1.4% | 0.7% |
| Gompertz | 1215.6 | 1222.6 | 30.7% | 1.8% | 0.0% | 0.0% | 0.0% |
| Log-logistic | 1184.8 | 1191.8 | 27.7% | 8.5% | 3.9% | 2.2% | 1.4% |
| Log-normal | 1181.1 | 1188.1 | 28.6% | 8.1% | 3.0% | 1.3% | 0.6% |
| Weibull | 1196.1 | 1203.1 | 28.9% | 3.0% | 0.2% | 0.0% | 0.0% |
| **Trifluridine-tipiracil + bevacizumab** | | | | | | | |
| Company clinical expert opinion | -- | -- | -- | 15-20% | -- | -- | 2.9%[B] |
| KM data | -- | -- | 45.1% | - | -- | -- | - |
| Exponential | 1120.5 | 1124.0 | 47.6% | 22.6% | 10.8% | 5.1% | 2.4% |
| Generalized gamma | 1084.3 | 1094.8 | 46.1% | 12.8% | 3.2% | 0.8% | 0.2% |
| Gompertz | 1099.9 | 1106.9 | 48.2% | 5.7% | 0.0% | 0.0% | 0.0% |
| Log-logistic | 1079.4 | 1086.4 | 45.1% | 16.6% | 8.0% | 4.6% | 2.9% |
| Log-normal | 1092.7 | 1099.7 | 46.5% | 19.7% | 9.7% | 5.3% | 3.1% |
| Weibull | 1084.9 | 1091.9 | 46.7% | 9.7% | 1.1% | 0.1% | 0.0% |

**Key:** AIC, Akaike information criteria; BIC, Bayesian information criteria; KM, Kaplan-Meier; OS, overall survival.
[A]EAG assumed interpretation of "few if any".
**[B]** On being provided with the output of the models, experts appeared to state that 2.9% was reasonable.
[C] Year 4 data obtained by EAG from the company economic model file for trifluridine-tipiracil + bevacizumab

*The company concluded that the log-logistic and log-normal curves have the best visual and statistical fit to the observed data and provided the most clinically plausible extrapolations for both treatment arms. However, the EAG considers all the curves, except Gompertz and exponential to be approximately equivalent in terms of visual and statistical fit. It is therefore unclear, for example why the generalised gamma was not considered as an appropriate option at this stage as it has very similar, and in the case of trifluridine monotherapy, has a slightly better AIC compared to the company preferred log-logistic curve as demonstrated in Table 15 above. Amongst the four plausible curves, the EAG agrees that the most appropriate decision on curve selection requires reliance on the plausibility of longer-term projections. However, the selection of curves based on expert opinion introduces uncertainty, particularly for the new intervention treatment as there is little experience with its use in a real-world setting. The EAG also notes that the experts were provided with the data before being asked to provide their views. This may have biased the opinions sought.*

*The EAG clinical expert is of the view that almost no patients will remain alive at 5 years, regardless of treatment arm and any treatment benefits would be observed at the start of the extrapolation phase. Our expert further explained that any projections over 1% at 5 years would lack face validity. These rules out the log-logistic curve for trifluridine-tipiracil monotherapy as well as both the log-normal and log-logistic for trifluridine-tipiracil + bevacizumab. The EAG is also concerned that the magnitude of the treatment effect at 2 years from fitting the log-logistic curve to both treatment arms (16.6% vs. 8.5% = 1.95) exceeds the observed treatment effect from the mature Kaplan Meier data at 1 year (45.1% vs.30% = 1.5). There is no evidence to support an increasing treatment effect over time and the EAG considers the company's approach to be overly optimistic given the available data.*

*The EAG considers the generalised gamma fitted to both treatment arms to be more appropriate. It provides good visual and statistical fit to the data, and has a steeper drop off in survival early in the extrapolation phase, in line with company and EAG expert opinion. The curves lead to a lower OS in bother arms (less than 1%) at 5 years, which aligns with the EAG's expert view. Whilst it may be deemed overly pessimistic that the OS curves for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy cross after 4 years, the impact of these crossing curves on life year gains is minimal due to the small proportion alive (<1% by year 5). The EAG and the company preferred OS curves are summarised in Figure 3.*

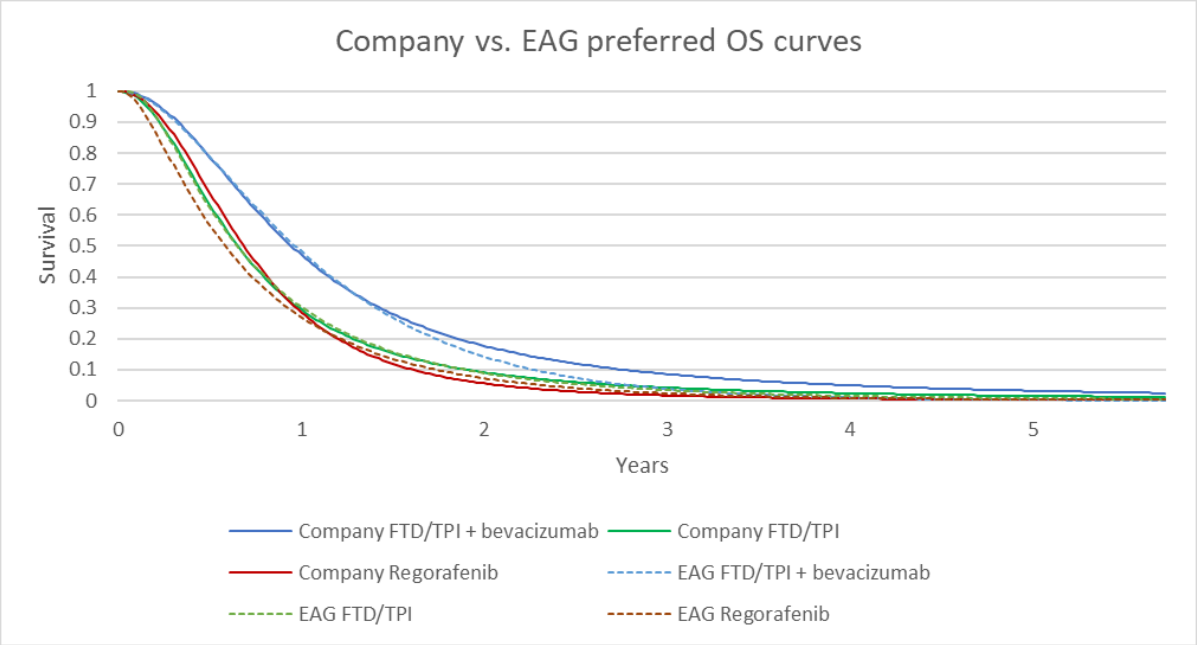



**Figure 3 EAG and company preferred overall survival curves.**

Regorafenib and best supportive care (BSC)

OS curves for regorafenib and BSC were obtained by applying HRs from the updated random-effects NMA post clarification (see Table 12, Chapter 3) to the preferred (log-logistic) trifluridine-tipiracil plus bevacizumab OS curve. The HRs applied were 0.60 (0.38, 0.95) and 0.41 (0.28,0.58) for trifluridine-tipiracil + bevacizumab compared to regorafenib and BSC respectively.

*The EAG notes that the approach taken for the company base case relies on applying a hazard ratio to an accelerated failure time survival curve for trifluridine-tipiracil + bevacizumab (i.e. log logistic in the company base case, or generalised gamma in the EAG preferred base case). For this approach to be robust, an assumption of proportional hazards is required, and this assumption is not met for accelerated failure time survival curves. This would imply that selecting a curve that aligns with proportional hazards such as exponential would be more appropriate, but the EAG also agrees with the company that exponential and Gompertz curves are not a good fit to the underlying trifluridine-tipiracil + bevacizumab data and produce unrealistic long-term OS estimates.*

*As an alternative solution, at clarification queries, the EAG requested whether there were any Kaplan Meier curves available for regorafenib from the literature that could be digitised to allow an independent survival curve to be fitted. The company helpfully identified data*

*from the CORRECT study for regorafenib.[18] The most appropriate parametric survival curve was selected based on assessing visual fit, statistical goodness of fit and clinical plausibility. The company identified generalised gamma as the most appropriate fit. The EAG agrees that in this scenario generalised gamma is most plausible and further notes that it is consistent with the EAG's preference for trifluridine-tipiracil monotherapy, which might be expected to have broadly similar survival trends.*

*However, the alternative approach also has limitations. As pointed out in the company's clarification response, it relies on a naïve comparison of the CORRECT and SUNLIGHT trials. [16 18] In order to help committee reach a decision on the most appropriate approach for modelling regorafenib overall survival, the EAG has compared the key available study baseline characteristics between the SUNLIGHT and CORRECT participants in Table 16 below. [16 18]*

**Table 16 Baseline characteristics of patients in the SUNLIGHT and CORRECT trials [adapted from Table 8, Document B of the CS]**

| | SUNLIGHT[16] | | CORRECT[18] | |
|---|---|---|---|---|
| **Characteristics** | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** | **Regorafenib (n=505)** | **Placebo (n=255)** |
| ***Demographics*** | | | | |
| Gender, n (%) | | | | |
| Male | 122 (49.6) | 134 (54.5) | 311 (62.0) | 153 (60.0) |
| Female | 124 (50.4) | 112 (45.5) | 194 (38.4) | 102 (40.0) |
| Age, median years (range) | 62 (20; 84) | 64 (24; 90) | 61 (IQR 54.0, 67.0) | 61 (IQR 54.0, 68.0) |
| <65, n (%) | 146 (59.3) | 129 (52.4) | NR | NR |
| ≥65, n (%) | 100 (40.7) | 117 (47.6) | NR | NR |
| Geographic Region, n (%) | | | | |
| North America | 8 (3.3) | 8 (3.3) | NR | NR |
| European Union | 158 (64.2) | 157 (63.8) | NR | NR |
| Rest of the World | 80 (32.5) | 81 (32.9) | NR | NR |
| North America, Western Europe, Israel, Australia | NR | NR | 420 (83.2) | 212 (83.1) |
| Asia | NR | NR | 69 (13.7) | 35 (13.7) |
| Eastern Europe | NR | NR | 16 (3.2) | 8 (3.1) |
| ***ECOG PS, n (%)*** | | | | |
| 0 | 119 (48.4) | 106 (43.1) | 265 (52.5) | 146 (57.3) |
| 1 | 127 (51.6) | 139 (56.5) | 240 (47.5) | 109 (42.7) |
| 2 | 0 | 1 (0.41)[a] | 0 (0) | 0 (0) |
| ***Primary site, n (%)*** | | | | |
| Colon | 180 (73.2) | 181 (73.6) | 323 (64.0)[c] | 172 (67.5) |

| | SUNLIGHT[16] | | CORRECT[18] | |
|---|---|---|---|---|
| **Characteristics** | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** | **Regorafenib (n=505)** | **Placebo (n=255)** |
| Rectum | 66 (26.8) | 65 (26.4) | 151 (29.9)[c] | 69 (27.1) |
| Colon and rectum | 0 (0) | 0 (0) | 30 (5.9)[c] | 14 (5.5) |
| ***Primary tumour location, n (%)*** | | | | |
| Right | 62 (25.2) | 77 (31.3) | NR | NR |
| Left | 184 (74.8) | 169 (68.7) | NR | NR |
| ***Number of metastatic organ sites, n (%)*** | | | | |
| 1-2 | 152 (61.8) | 141 (57.3) | NR | NR |
| ≥3 | 94 (38.2) | 105 (42.7) | NR | NR |
| ***Previous metastatic drug treatment, n (%)*** | | | | |
| Fluoropyrimidine | 246 (100) | 246 (100) | NR | NR |
| Irinotecan | 246 (100) | 245 (99.6) | NR | NR |
| Oxaliplatin | 241 (98.0) | 243 (98.8) | NR | NR |
| Anti-VEGF | 178 (72.4) | 176 (71.5) | NR | NR |
| Anti-EGFR in *RAS* WT* | 67/71 (94.4) | 66/71 (93.0) | NR | NR |
| ***Number of prior metastatic drug regimens, n (%)*** | | | | |
| 1 | 11 (4.5) | 15 (6.1) | NR | NR |
| 2 | 229 (93.1) | 224 (91.1) | NR | NR |
| ≥ 3 | 6 (2.4) | 7 (2.8) | NR | NR |
| 1-2 | NR | NR | 135 (26.7) | 63 (24.7) |
| 3 | NR | NR | 125 (24.8) | 72 (28.2) |
| ≥ 4 | NR | NR | 245 (48.5) | 120 (47.1) |
| ***Tumour mutational status, n (%)*** | | | | |
| *RAS* | | | | |

| | SUNLIGHT[16] | | CORRECT[18] | |
|---|---|---|---|---|
| **Characteristics** | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** | **Regorafenib (n=505)** | **Placebo (n=255)** |
| Mutant | 171 (69.5) | 170 (69.1) | NR | NR |
| WT | 75 (30.5) | 76 (30.9) | NR | NR |
| *BRAF* | | | | |
| Mutant | 8 (3.3) | 11 (4.5) | 14/336 (4.2) | 3/166 (1.8) |
| WT | 159 (64.6) | 156 (63.4) | NR | NR |
| Unknown/Missing data | 79 (32.1) | 79 (32.1) | NR | NR |
| MMR/MSI | | | | |
| MSI/high/MMR deficient | 13 (5.3) | 8 (3.3) | NR | NR |
| MSS/MSI low/MMR proficient | 139 (56.5) | 145 (58.9) | NR | NR |
| Unknown/Missing data | 94 (38.2) | 93 (37.8) | NR | NR |
| ***Site of metastasis, n (%)[b]*** | | | | |
| Liver | 194 (78.86) | 188 (76.42) | NR | NR |
| Lung | 157 (63.82) | 154 (62.60) | NR | NR |
| Lymph node | 95 (38.62) | 101 (41.06) | NR | NR |
| Peritoneal | 60 (24.39) | 60 (24.39) | NR | NR |
| Soft tissue | 9 (3.66) | 9 (3.66) | NR | NR |
| Bone | 22 (8.94) | 30 (12.20) | NR | NR |
| Brain | 2 (0.81) | 0 | NR | NR |
| Skin | 0 | 1 (0.41) | NR | NR |
| Other | 31 (12.60) | 38 (15.45) | NR | NR |
| ***Prior treatment with bevacizumab, n (%)[b]*** | | | | |

| | SUNLIGHT[16] | | CORRECT[18] | |
|---|---|---|---|---|
| **Characteristics** | **Trifluridine-tipiracil + bevacizumab (n=246)** | **Trifluridine-tipiracil (n=246)** | **Regorafenib (n=505)** | **Placebo (n=255)** |
| No | 68 (27.64) | 70 (28.46) | 0 (0) | 0 (0) |
| Yes | 178 (72.36) | 176 (71.54) | 505 (100.0) | 255 (100.0) |

**Note**: Data was used until 19 July 2022. Percentages are based on N, except (*) based on the number of patients for whom RAS Status was wild-type. [a]One patient had an ECOG PS rated 2 at baseline prior to treatment while it was rated 1 at inclusion; [b]data from CSR; [c]Information missing for one participant.

**Key**: BRAF, V-raf murine sarcoma viral oncogene homolog B; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MSI, microsatellite instability; MMR, mismatch repair; MSS, microsatellite stable; N/A, not applicable; PS, performance status; RAS, Rat sarcoma virus; SD, standard deviation; VEGF, vascular endothelial growth factor; WT, wild-type

*Key differences between the studies are that regorafenib patients appear to have had a greater number of prior metastatic drug regimens than in SUNLIGHT, and all participants in CORRECT had prior bevacizumab treatment. This might suggest CORRECT patients had more severe disease, thus potentially biasing the comparison in favour of trifluridine-tipiracil + bevacizumab. Similarly, given that all CORRECT patients had previous bevacizumab, the results of the company's subgroup analyses suggest this may also be biased in favour of trifluridine-tipiracil + bevacizumab. However, the overall magnitude of any biases is likely to be uncertain, particularly given that the definition of previous lines of treatment may vary across studies. Neither approach to estimating regorafenib OS is ideal, and both are associated with limitations. Both approaches should be considered for decision making. However, the EAG considers the naïve comparison is less likely to be biased and is therefore used in our base case. Given that independent curves for BSC were not provided to the EAG, the base-case analysis continues to BSC HRs from the NMA. The EAG note that using the NMA HRs has the same limitations as outlined for regorafenib. The EAG would be happy to consider independent curves for BSC should the company wish to provide these data.*

***PFS***

Trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy

A similar approach is taken to fit PFS curves as described above for OS. Several curves fit the data reasonably well (generalised gamma, log-logistic and log-normal). The company observed some minor under- and over-estimating throughout due to 'steps' in the observed Kaplan Meier data likely caused by the protocol-driven assessments of progression in the SUNLIGHT trial.[16] In terms of clinical expectations, for trifluridine-tipiracil monotherapy, clinical experts expected no patients or less than 0.2% to remain progression free at 2 years and highlighted the log-normal curve as a potential plausible option. For trifluridine-tipiracil plus bevacizumab, clinicians highlighted log-logistic or log-normal generating plausible extrapolations. One clinician highlighted that they would expect a maximum of 2% progression-free at 3-years. Statistical fit and modelled proportion progression-free up to 5 years are compared for each parametric survival curve in Table 17. The company select the log-normal for the base case analysis for both treatment arms.

*The EAG is satisfied that the company's approach to selecting an appropriate PFS curve is appropriate and that all survival curves generate similar long-term outcomes and the impact of choice of curve on the ICER is minimal.*

**Table 17 Comparison of statistical goodness of fit, company clinical expert opinion and modelled outcomes for trifluridine-tipiracil monotherapy and trifluridine-tipiracil + bevacizumab progression-free survival for different parametric survival curves**

| Model | Statistical fit | | PFS landmarks (years) | | | | |
|---|---|---|---|---|---|---|---|
| | AIC | BIC | 1 | 2 | 3 | 4 | 5 |
| **Trifluridine-tipiracil monotherapy** | | | | | | | |
| Company clinical expert opinion | -- | -- | -- | <1% | 0% | 0% | 0% |
| KM data | -- | -- | 1.0% | - | - | - | - |
| Exponential | 1095.1 | 1098.6 | 4.0% | 0.2% | 0.0% | 0.0% | 0.0% |
| Generalized gamma | 975.3 | 985.8 | 2.7% | 0.4% | 0.1% | 0.0% | 0.0% |
| Gompertz | 1076.5 | 1083.5 | 1.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Log-logistic | 990.4 | 997.4 | 2.2% | 0.4% | 0.1% | 0.1% | 0.0% |
| Log-normal | 981.3 | 988.3 | 1.5% | 0.1% | 0.0% | 0.0% | 0.0% |
| Weibull | 1035.1 | 1042.2 | 0.7% | 0.0% | 0.0% | 0.0% | 0.0% |
| **Trifluridine-tipiracil + bevacizumab** | | | | | | | |
| Company clinical expert opinion | -- | -- | -- | -- | 2% | -- | -- |
| KM data | -- | -- | 16.1% | - | - | - | - |
| Exponential | 1235.1 | 1238.6 | 19.6% | 3.8% | 0.8% | 0.1% | 0.0% |
| Generalized gamma | 1195.9 | 1206.4 | 16.1% | 2.9% | 0.7% | 0.2% | 0.1% |
| Gompertz | 1226.1 | 1233.2 | 16.7% | 0.4% | 0.0% | 0.0% | 0.0% |
| Log-logistic | 1196.4 | 1203.4 | 16.3% | 4.7% | 2.2% | 1.2% | 0.8% |
| Log-normal | 1195.3 | 1202.3 | 16.9% | 3.9% | 1.3% | 0.5% | 0.2% |
| Weibull | 1208.5 | 1215.5 | 15.1% | 0.7% | 0.0% | 0.0% | 0.0% |

**Key:** AIC, Akaike information criteria; BIC, Bayesian information criteria; KM, Kaplan-Meier; PFS, progression-free survival.

Regorafenib and BSC

For regorafenib and BSC, as with OS, the HR derived from the NMA was applied to the independently fitted trifluridine-tipiracil plus bevacizumab PFS curve. From the preferred base case random-effects NMA for PFS (updated post clarification queries), hazard ratios of 0.49 (0.31,0.84) and 0.21 (0.14,0.31) were applied to regorafenib and BSC respectively.

*As with overall survival, following clarification queries, the company provided digitised KM curve data from the CORRECT study for regorafenib. They selected a generalised gamma curve for the scenario analysis, in line with the preference of the committee from TA866. The EAG is satisfied that the curve selection process for regorafenib PFS is appropriate in this scenario analysis. Despite the limitations of a naïve comparison across studies, the EAG consider it more appropriate to choose this approach as opposed to applying HRs to an accelerated failure time curve. The company and the EAG's preferred PFS curves are compared in Figure 4.*

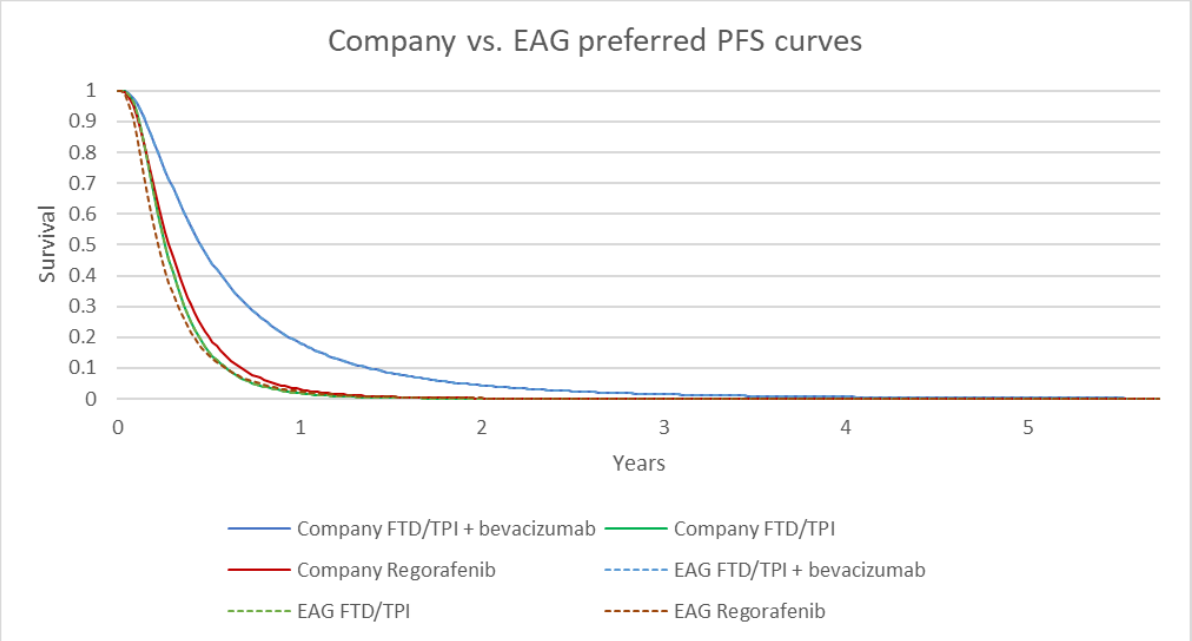



**Figure 4 EAG and company preferred progression-free survival curves.**

***Time on treatment (ToT)***

For trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy, treatment acquisition and administration costs were derived from treatment discontinuation curves fitted to ToT KM data from the SUNLIGHT study.[16] For the combination of trifluridine-tipiracil + bevacizumab, patients could stop bevacizumab before trifluridine-tipiracil.

Therefore, the combination treatment components were considered separately for fitting treatment discontinuation curves. The overall process of selecting the most appropriate parametric survival curve followed the methods described for OS, assessing visual and statistical goodness of fit using AIC and BIC scores (See Table 37 of the company submission). Weibull provided the best statistical goodness of fit for both intervention combination treatments and either log-normal or generalised gamma was the best fit for the trifluridine-monotherapy arm. As very little extrapolation is required given the maturity of the data, the company chose the curves with the best statistical fit (Weibull for both combination treatments and generalised gamma for trifluridine-tipiracil monotherapy).

*The EAG is satisfied that the company's approach to fitting TOT curves for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil is appropriate. At clarification, the EAG queried whether the PFS and TOT curves for trifluridine-tipiracil monotherapy crossed for a small proportion of patients due to the uncertainty in extrapolation. The company confirmed that the model caps TOT at PFS to ensure that treatment does not continue beyond progression. The EAG considers the company's capping of ToT at PFS to be appropriate.*

For regorafenib, data are not publicly available that would have allowed the company to fit ToT curves directly to observed data, nor were sufficient data available to inform an NMA. The company base case analysis, therefore, assumed that TOT for regorafenib was equal to PFS for regorafenib in the absence of available data because the SmPC recommends treatment until progression, unless discontinuation is required due to unacceptable toxicity, and because the approach is consistent with the approach taken for TA866.[24] In light of company sought expert opinion that regorafenib may be stopped prior to progression in UK clinical practice, a scenario analysis was provided that applied the PFS HR (trifluridine-tipiracil + bevacizumab vs. regorafenib) as an alternative way to estimate the ToT curve.

*The EAG's clinical expert agrees with the company's expert opinion that regorafenib may be stopped early due to unacceptable toxicity and that there may be a period of time after discontinuation before progression. The EAG is concerned that the company's preferred base case approach is likely to overestimate the treatment acquisition costs for regorafenib. The EAG is aware that the committee for TA866 may have had access to confidential ToT data for the regorafenib appraisal. However, in the absence of access to ToT KM curves, the EAG has considered the outputs of several alternative modelling assumptions to generate ToT. Each of*

*these approaches is described in Table 18 below and an assessment of the face validity of the modelled outputs against mean and median ToT from the CORRECT study is provided.*[18] *Data are assessed against the CORRECT, rather than the CONCUR study for regorafenib because the former are used to estimate the PFS curves in the EAG base case, and it is important to ensure consistency between data sources for comparison.*

*The EAG's preferred approach is to assume that a proportion of the progression-free patients at any one time are on treatment. This proportion is calculated as the mean ToT from the CORRECT study (2.8 months, or 12.2 weeks) divided by the mean modelled PFS (18.02 weeks in the company preferred base case analysis), leading to a proportion of the progression-free cohort on treatment equal to 68%. The mean modelled PFS is used because the mean PFS from the CORRECT study is not publicly available. The EAG and the company's preferred treatment discontinuation curves are compared in Figure 5. The EAG's preferred approach provides the best face validity in terms of reported median and mean ToT from the CORRECT study as shown in Table 18 below.* [18] *An alternative approach to estimate a ToT curve for regorafenib would be to use the median data from the CORRECT study and fit an exponential distribution (See Chapter 6, scenario analysis).*

**Figure 5 EAG and company preferred time to treatment discontinuation curves.**

**Table 18 Alternative approaches for calculating regorafenib time on treatment curves.**

| Regorafenib time on treatment approach | Median (weeks) | Mean (weeks) |
|---|---|---|
| CORRECT study[18] [A] | 7.4 | 12.2 |
| Company preferred base case model | 14.0 | 18.0 |
| Company scenario analysis (Apply PFS HR for trifluridine-tipiracil + bevacizumab vs. regorafenib to the TTD curve) | 14.0 | 16.8 |
| EAG alternative model 1 (assume that the proportion of the regorafenib progression-free cohort on treatment is equal to the proportion for trifluridine-tipiracil monotherapy) | 12.2 | 16.7 |
| EAG alternative model 2 (assume that the proportion of those progression-free on treatment is equal to the median ToT / median PFS from the CORRECT study – 0.89) [18] | 12.5 | 16.1 |
| **EAG preferred approach (assume that the proportion of those progression-free on treatment is equal to the mean ToT from the CORRECT study / modelled mean PFS – 0.68)** [B] [18] | **8.8** | **12.2** |

[A] Calculated from monthly data reported in the CORRECT study (median: 1.7 months; mean: 2.8 months) [18] [B] Note: data reported in the table are applied to the company's preferred base case configurations. The proportion on treatment will adapt dynamically with regorafenib PFS parameters. For example, the proportion in the EAG's preferred base case is 0.80, leading to similar modelled median and mean ToT.
**Key:** HR, hazard ratio; PFS, progression-free survival; ToT, time on treatment; TTD, time to treatment discontinuation

### 4.2.7 Health-related quality of life

The company conducted a systematic literature review to identify relevant published HRQL data for advanced or mCRC after two prior chemotherapy regimens (See section B.3.4.1 and B.3.4.2 of the company submission). Twenty-nine reports describing 18 unique studies were included in the systematic literature review. Of these 18 studies, 11 were randomised control trials, one was a single-arm trial, and six were observational studies. Four studies reported EQ-5D utility data, two of which reported utility values associated with health states relevant to the model structure. However, none of the values from the literature were deemed suitable because they related to different treatments or different places in the pathway. The company therefore estimated treatment-dependent health state utility values for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy using EQ-5D-5L data collected from the SUNLIGHT study. EQ-5D-5L data were mapped to the 3L version using the Hernández-

Alava et al algorithm[28] and valued using UK utility tariffs. The company used utility values reported by previous TAs (TA405 and TA866) in scenario analysis.[24, 29]

*The EAG is satisfied that utility data obtained from the SUNLIGHT study are appropriate for decision making in this patient population. The mapping approach and valuation of HSUVs are in line with the NICE reference case. All utilities in the model were appropriately age-adjusted to account for the natural decline in quality of life associated with age.*

For the company base case analysis, treatment-dependent (for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy) health state utility values are applied according to progression status (progression-free, progressed). At clarification, the EAG asked the company to expand Table 39 of their submission to report the raw data from the SUNLIGHT study for HSUVs stratified by health state (pre- and post-progression) and by treatment arm. These data can be found in Table 19 below.

**Table 19 Summary of SUNLIGHT health state utility values, by treatment arm and health state [reproduced from Table 39 of the CS and Table 12 of the company's clarification response]**

| Health state | Number of patients | Number of observations | Mean (SD) | Median (IQR) |
|---|---|---|---|---|
| **Pooled data from the SUNLIGHT study** | | | | |
| Progression-free | 447 | 1,975 | 0.794 (0.190) | 0.820 (0.246 – 0.989) |
| Progressed | 270 | 304 | 0.703 (0.238) | 0.737 (0.066 – 0.989) |
| **Trifluridine-tipiracil with bevacizumab arm** | | | | |
| Progression-free | 232 | 1,298 | 0.800 (0.189) | 0.836 (0.692 – 0.986) |
| Progressed | 126 | 143 | 0.729 (0.197) | 0.747 (0.624 – 0.867) |
| **Trifluridine-tipiracil arm** | | | | |
| Progression-free | 215 | 677 | 0.782 (0.218) | 0.810 (0.694 – 0.985) |
| Progressed | 144 | 161 | 0.679 (0.268) | 0.723 (0.563 – 0.864) |

**Key:** IQR, interquartile range; SD, standard deviation

Two mixed-effect regression models were then explored in the original submission to assign treatment-dependent HSUVs for pre- and post-progression model states. The first estimated treatment-independent utilities and the latter (base case) estimated treatment-dependent utilities by including treatment arm and progression status as independent variables. The models were estimated using EQ-5D scores from all available data time points. At clarification, the EAG asked the company to provide re-analysis of the trial data using a repeated measures model, including covariates for baseline EQ-5D utility and an interaction term between health state and treatment. Five mixed-effects regression models were provided to estimate utilities:

1. Model 1: included progression status as an independent variable (treatment pooled HSUVs)
2. Model 2: included randomised arm and progression status (treatment dependent HSUVs applied in the company's base case analysis)
3. Model 3: included treatment arm, progression status and an interaction term for treatment x health state.
4. Model 4: included baseline utility, treatment arm, progression status and an interaction term for treatment x health state.
5. Model 5: provided by the company following an additional EAG's request, as per model 2, with the addition of baseline utility as an independent variable in the model.

The results of the original and revised models are summarised in Table 20 below.

**Table 20 Results of different mixed effects regression models to estimate health state utility values (reproduced from Table 15 of the company's clarification response)**

| Coefficient | Value | SE | p-value |
|---|---|---|---|
| **Model 1** | | | |
| Intercept | 0.681 | 0.013 | 0.000 |
| Progression-free | 0.078 | 0.011 | 0.000 |
| **Model 2** | | | |
| Intercept | 0.659 | 0.016 | 0.000 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.043 | 0.018 | 0.021 |
| Progression-free | 0.077 | 0.011 | 0.000 |
| **Model 3** | | | |
| Intercept | 0.655 | 0.182 | 0.000 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.050 | 0.026 | 0.053 |
| Progression-free | 0.082 | 0.015 | 0.000 |
| Interaction term: Treatment arm: Trifluridine-tipiracil plus bevacizumab * Progression-free | -0.009 | 0.022 | 0.670 |
| **Model 4** | | | |
| Intercept | 0.036 | 0.023 | 0.129 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | 0.007 | 0.023 | 0.748 |
| Progression-free | 0.080 | 0.015 | 0.000 |
| Interaction term: Treatment arm: Trifluridine-tipiracil plus bevacizumab * Progression-free | -0.011 | 0.022 | 0.619 |
| Baseline utility | 0.833 | 0.023 | 0.000 |
| **Model 5 (as per Model 2, with the addition of baseline utility)** | | | |
| Intercept | 0.040 | 0.021 | 0.060 |
| Treatment arm: Trifluridine-tipiracil plus bevacizumab | -0.003 | 0.010 | 0.755 |
| Progression-free | 0.075 | 0.011 | 0.000 |
| Baseline utility | 0.833 | 0.023 | 0.000 |

**Key:** AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error

The company note that alternative models (Models 1 – 3) have similar results and that the addition of the interactive term in Model 3 does not substantially impact the resulting utility values. The company note that the values from Model 4 result in a higher progression-free utility value for the trifluridine-tipiracil monotherapy compared to trifluridine-tipiracil plus bevacizumab (0.741 vs 0.745, respectively) which is counterintuitive to the clinical expectation (and therefore should be interpreted with caution). Therefore, the company believe the original base case model (Model 2) to be the most appropriate to inform treatment-specific utility values.

*At clarification stage, the EAG asked the company to provide the results of a repeated measures model, but it is unclear whether the results provided in the company's clarification response are from the original mixed effects model or a revised repeated measures modelling approach. The original EAG report noted that further clarification on this point would be appreciated. The company responded at factual accuracy check, noting that the model was implemented in R, using the "lmer" function and as such incorporated repeated measures into the utility models. The EAG is satisfied with the company's additional clarification on this point.*

*The EAG notes that the interaction terms between treatment arm and health state are not statistically significant, which indicates that treatment-specific utility values are not supported by the regression modelling conducted by the company. In the initial clarification response, the EAG noted that the company's preferred Model 2 had not been adjusted for baseline utility. Following an additional request, this was provided by the company (Model 5 above). The EAG notes that adjusting for baseline utility removes the significant treatment effect from the model.*

*Given that the interaction terms do not support a significant treatment effect within state, adjustment for baseline utility removes any apparent treatment effect. The EAG is of the view that treatment-dependent health state utility values are not appropriate for this assessment. The EAG's preferred base case, therefore, uses treatment pooled health state utility values estimated from Model 1.*

***Clinical rationale:***

In response to clarification queries (B5), the company provided further elaboration on their clinical expert elicitation, confirming that all experts were in favour of a higher utility for trifluridine-tipiracil + bevacizumab than trifluridine-tipiracil alone in the progression-free health state. The company justified this on the grounds of a higher overall response rate for trifluridine-tipiracil + bevacizumab (ORR: 6.1%) compared with trifluridine-tipiracil monotherapy (ORR: 1.2%). Following the EAG's clarification request, additional clinical data were provided to support the company's position (See figures 4 and 5, as well as table 15 of the clarification response).

*The EAG agrees that Figures 4 and 5 of the clarification response show a clear benefit for trifluridine-tipiracil + bevacizumab vs. trifluridine-tipiracil monotherapy with respect to time to deterioration as defined using the QLQ-C30 instrument. However, these data do not appear to be treatment-specific and may therefore simply signify the benefits of reduced time to progression as opposed to any within-state benefit for trifluridine-tipiracil + bevacizumab. The EAG considers the data provided in Table 14 of the company's clarification response to be more helpful in reaching a conclusion regarding the utility impact by health state. Incremental utilities by treatment arm in each state appear small in magnitude with large standard deviations which would likely preclude a statistically significant treatment effect within state for the EORTC QLQ-C30.*

The company also note that the clinical expert opinion was more varied with respect to any additional benefit post-progression. They raise a concern that accepting treatment dependent utilities for the progression-free, but not the progressed state would lead to counterintuitive results by creating a larger decrement post progression in the trifluridine-tipiracil + bevacizumab arm than in the trifluridine-tipiracil monotherapy arm of the model.

*The EAG agrees with the company regarding the concerns about counterintuitive results. As such the EAG believe that the same approach should be taken for both the pre-progression and post-progression health state utility values and that the same decline post progression should be modelled for both treatment arms. However, the EAG is not satisfied that the utility regression models, or the additional supportive data are sufficiently strong to justify the use of treatment-dependent utilities in the model. The EAG, therefore, prefers the use of treatment pooled health state utility values. The EAG's approach also maintains consistency with the preferred approach to integrating post-progression treatment costs in the model (See Section 4.2.8).*

The company assume that regorafenib and BSC have the same health state utilities values as the trifluridine-tipiracil monotherapy arm. The company justified their simplifying assumption as being appropriate given the similarity in outcomes (OS and PFS; see section B.3.3.2 of the company submission) between regorafenib and trifluridine-tipiracil. The company state that this may over-estimate the HSUVs for regorafenib because of toxicity concerns but notes that the utility impacts associated with AEs are captured separately.

*The EAG agrees that the company's decision not to adjust the HSUVs for regorafenib is appropriate given that the utility implications of toxicity are already captured in the AE disutilities. The EAG is satisfied that the company's approach to assigning the same HSUVs to regorafenib and trifluridine-tipiracil is appropriate but notes that any resultant bias due to underestimating utility losses due to additional toxicity would likely favour regorafenib in the economic model.*

*The EAG and the company's preferred HSUVs are compared in Table 21 below. The EAG also noted a minor typographical error in the company submission, table 45, which was also corrected post clarification (see Table 20 in the company's clarification response). The EAG is satisfied that the corrected data are now available, and that the data included in the model are an accurate reflection of the methods described in the submission documentation.*

**Table 21 Summary of company and EAG's preferred HSUVs**

| State | Treatment | Utility value | 95% confidence interval | Source |
|---|---|---|---|---|
| Company derived HSUVs | | | | |
| Progression-free | Trifluridine-tipiracil + bevacizumab | 0.779 | 0.746 - 0.813 | Treatment-dependent HSUVs derived from SUNLIGHT [16] |
| | Trifluridine-tipiracil | 0.737 | 0.712 - 0.762 | |
| | Regorafenib | 0.737 | 0.712 - 0.762 | |
| | BSC | 0.737 | 0.712 - 0.762 | |
| Progressed disease | Trifluridine-tipiracil + bevacizumab | 0.702 | 0.662 - 0.742 | |
| | Trifluridine-tipiracil | 0.659 | 0.628 - 0.691 | |
| | Regorafenib [A] | 0.659 | 0.712 - 0.762 | |
| | BSC [A] | 0.659 | 0.712 - 0.762 | |
| EAG's preferred HSUVs | | | | |
| Progression-free | All | 0.759 | 0.734 - 0.785 | Treatment pooled HSUVs derived from SUNLIGHT [16] |
| Progressed disease | All | 0.681 | 0.655 - 0.707 | |

**Key:** BSC, best supportive care

[A] Had minor typographical error in the original submission documentation. Correct values are provided here.

***Utility impact of adverse reactions***

Adverse event disutilities were applied as a one-off QALY loss in the first model cycle for all treatment arms based on the event probability, duration and assigned event-specific disutility. All adverse events of grade 3 or above, observed in at least 2% of either arm of the SUNLIGHT study were included.[16] Adverse events for regorafenib and BSC were sourced from TA866, based on pooled CORRECT and CONCUR study data.[18] Incidence, duration, and disutility applied to each adverse event are summarised across modelled treatment arms in Table 22. The disutility values applied to each adverse event were identified from published literature.[30-32]

*The EAG agrees that the measures taken to generate adverse event disutilities appear to be reasonable. There is some concern that the approach to incorporating AEs as a one-off QALY loss in the model may fail to capture the impact of recurrent events. However, applying an adverse event disutility across each cycle is unlikely to have a major impact on the ICER because the EAG's clinical expert is of the view that AEs usually occur early in the treatment cycle and time to progression is relatively short across all treatments. The EAG asked for further details of disutility sources for each adverse event, and this was provided in clarification response B6. The EAG is satisfied that the sources of AE disutilities are appropriate.*

**Table 22 Incidence, duration, and disutility of Grade ≥ 3 adverse events occurring in ≥2% of SUNLIGHT trial participants (reproduced from Tables 38 and 43 of the CS)**

| Adverse event | Trifluridine-tipiracil + bevacizumab[16] | Trifluridine-tipiracil[16] | BSC[24] | Regorafenib[24] | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|---|---|---|---|
| Abdominal pain | 2.0% | 1.6% | - | - | -0.0468 | 15.6 | Assumed the same as diarrhoea | SUNLIGHT[16] |
| Alanine aminotransferase increased | 2.8% | - | - | - | -0.08973 | 26.7 | Assumed equal to neutropenia | SUNLIGHT[16] |
| Anaemia | 6.1% | 11.0% | - | 2.20% | -0.0209 | 118.8 | Sullivan et al 2006[72] | SUNLIGHT[16] |
| Anorexia | - | - | 2.20% | 2.50% | -0.0468 | 11.8 | Assumed same as diarrhoea | Average of all AE in SUNLIGHT[16] |
| Aspartate aminotransferase increased | 2.4% | 1.2% | - | - | -0.08973 | 14.0 | Assumed equal to neutropenia | SUNLIGHT[16] |
| Asthenia | 4.1% | 4.1% | - | - | -0.07346 | 27.6 | Assumed equal to fatigue | SUNLIGHT[16] |
| Diarrhoea | 0.8% | 2.4% | 0.60% | 5.70% | -0.0468 | 31.9 | Nafees et al, 2008[73] | SUNLIGHT[16] |
| Fatigue | 1.2% | 3.7% | 4.40% | 8.20% | -0.07346 | 6.3 | Nafees et al, 2008[73] | SUNLIGHT[16] |
| Febrile neutropenia | 0.4% | 2.0% | - | - | -0.15 | 16.2 | Lloyd et al, 2006[74] | SUNLIGHT[16] |

| Adverse event | Trifluridine-tipiracil + bevacizumab[16] | Trifluridine-tipiracil[16] | BSC[24] | Regorafenib[24] | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|---|---|---|---|
| Hand foot skin reaction | - | - | 0.30% | 16.50% | -0.116 | 11.8 | Lloyd et al, 2006[74] | Average of all AE in SUNLIGHT[16] |
| Hepatic failure | - | 2.4% | - | - | -0.0567 | 7.3 | Sullivan et al 2006[72] | SUNLIGHT[16] |
| Hyperbilirubinaemia | 1.6% | 1.2% | 0.90% | 3.00% | -0.08973 | 39.0 | Assumed equal to neutropenia | SUNLIGHT[16] |
| Hypertension | 5.7% | 1.2% | 1.20% | 8.00% | -0.025 | 21.1 | Sullivan et al 2006[72] | SUNLIGHT[16] |
| Hypophosphataemia | - | - | 0.30% | 4.40% | -0.0359 | 11.8 | Sullivan et al 2006[72] | Average of all AE in SUNLIGHT[16] |
| Intestinal obstruction | 2.8% | 1.6% | - | - | -0.0193 | 9.2 | Sullivan et al 2006[72] | SUNLIGHT[16] |
| Jaundice | 1.6% | 2.0% | - | - | -0.07346 | 16.5 | Assumed equal to fatigue | SUNLIGHT[16] |
| Leukopenia | 1.6% | 2.8% | - | - | -0.08973 | 20.8 | Assumed equal to neutropenia | SUNLIGHT[16] |
| Lipase increased | - | - | 0.60% | 3.50% | -0.08973 | 11.8 | Assumed equal to neutropenia | Average of all AE in SUNLIGHT[16] |
| Malignant neoplasm progression | 2.4% | 4.1% | - | - | -0.069 | 9.9 | Assumed the same as pain | SUNLIGHT[16] |

| Adverse event | Trifluridine-tipiracil + bevacizumab[16] | Trifluridine-tipiracil[16] | BSC[24] | Regorafenib[24] | Disutility | Duration (days) | Source for disutility | Source for duration |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | (Doyle et al, 2008)[75] | |
| Mucositis | - | - | 0.19% | 2.40% | -0.03248 | 11.8 | Assumed the same as rash | Average of all AE in SUNLIGHT[16] |
| Neutropenia | 43.1% | 32.1% | - | - | -0.08973 | 11.8 | Nafees et al, 2008 | SUNLIGHT[16] |
| Neutrophil count decreased | 8.9% | 5.3% | - | - | -0.08973 | 14.6 | Assumed equal to neutropenia | SUNLIGHT[16] |
| Pulmonary embolism | 0.8% | 2.0% | - | - | -0.186 | 70.7 | Hunter et al, 2015 | SUNLIGHT[16] |
| Rash | - | - | - | 5.50% | -0.03248 | 11.8 | Nafees et al, 2008 | Average of all AE in SUNLIGHT[16] |
| Thrombocytopenia | 2.8% | 1.2% | 0.30% | 2.80% | -0.08973 | 34.6 | Assumed equal to neutropenia | SUNLIGHT[16] |

**Key:** AE, adverse events; BSC, best supportive care; TA, technology appraisal

### 4.2.8 Resources and costs

The company conducted a systematic literature search to inform healthcare resource use and costs from previously treated mCRC in the third-line setting. Full details of the review are presented in Appendix I of the company submission. None of the studies were considered relevant however the company used estimates from prior NICE appraisals (TA405 and TA886)[24, 29] to inform the resource use and costs.

***Treatment acquisition costs***

The dosing schedule for each treatment was taken from the respective treatment's summary of product characteristics (SmPC) and a summary of dosing and cost per dose is provided in Table 48 of the company submission. The treatment acquisition costs for trifluridine-tipiracil oral monotherapy are calculated based on a dose of 35mg/m$^2$ of body surface area (BSA), twice daily on days 1 to 5 and 8-12 in a 28-day treatment cycle. The BSA distribution, fitted using a log-normal distribution was derived from the SUNLIGHT trial to calculate the average cost per dose. Bevacizumab is administered intravenously every 2 weeks, according to patient weight, at a dose of 5mg/kg. The average number of vials is derived from patient-level data in the SUNLIGHT trial and accounts for vial wastage. Regorafenib is administered orally at 160mg per day for the first 3-weeks of a 4-weekly cycle. BSC incurs no treatment acquisition costs. The unit costs (See Table 46 of the company submission) are based on drug tariff prices, sourced from the British National Formulary (BNF) in the absence of eMIT price data.[33] There is an approved PAS for trifluridine-tipiracil of [redacted]% which is incorporated throughout the results section. Confidential discounts are available for regorafenib and bevacizumab and these are considered in a confidential appendix to the EAG report.

To account for the impact of dose reductions, missed doses, and treatment interruptions, treatment acquisition costs were multiplied by the following relative dose intensities (RDI), based on data from the SUNLIGHT study (trifluridine-tipiracil, as part of combination treatment: 0.850; bevacizumab: 0.869; trifluridine-tipiracil monotherapy: 0.8725 and regorafenib: 0.8725).[16] The company base case analysis assumed that the RDI for regorafenib was equal to that of trifluridine-tipiracil monotherapy, and a scenario analysis explored the use of an RDI = 0.789, obtained from the CORRECT study.[18]

*The EAG considered the company's general costing approach to be appropriate and is satisfied that wastage has been accounted for in treatment acquisition cost calculations.*

*However, the EAG prefers the company's scenario analysis for regorafenib RDI because clinical expert opinion sought by the EAG and company both suggest that dose interruptions and reductions are more common for regorafenib than for trifluridine-tipiracil. This is confirmed by the lower RDI reported in the CORRECT study. The EAG prefers to use a RDI of 0.789 for the base case analysis. This approach maintains consistency with the EAG's general approach of preferring time on treatment and PFS data for regorafenib sourced from the CORRECT study.*[18]

*The EAG also asked for confirmation that modelled BSC costs include all resource use likely to be incurred due to concomitant treatments, monitoring, and management of symptoms in UK clinical practice and whether any expert advice had been sought regarding the plausibility of the modelled BSC costs. The company acknowledged that there may be some costs incurred by BSC patients for concomitant medicines, however, the costs of these treatments are likely to be small and could be accounted for in all treatment arms. Therefore, it was conservatively assumed that the incremental BSC costs have been captured within resource use already costed. This is also the approach used in prior NICE appraisals in mCRC.*[17,34] *The company provided a scenario, aligned with a scenario explored in TA866, applying an additional weekly cost of £12.50 for BSC. The EAG agrees with the scenario analysis approach taken by the company and include this in our preferred base case assumptions.*

***Treatment administration costs***

For oral therapies, no administration costs are included as they are assumed to be captured by routine visits in line with assumptions made in prior appraisals.[24] An additional cost of £286.71 (SB12Z - deliver simple parenteral chemotherapy at first attendance) was applied every two weeks for bevacizumab.

*The EAG queried why administration costs based on the cost of a 'first attendance' were applied for each subsequent dose in the model (i.e., every two weeks for bevacizumab). The company provided a scenario analysis that separated initial and subsequent attendances obtained from the 2023/24 NHS Payment Scheme. Initial attendance was assigned a cost of £167 (HRG code: SB12Z) and subsequent attendance was assigned a cost of £334 (HRG code SB15Z). The EAG notes that the costing year and underlying source of unit costs are different to those considered in the rest of the submission. Furthermore, the subsequent costs*

*are higher than the initial costs, likely because the subsequent chemotherapy delivery HRG code SB15Z covers a range of complexity of subsequent treatments, whereas the initial administration code (SB12Z) covers simple parenteral chemotherapy. The EAG would expect the costs of subsequent deliveries to be lower, as they likely require a shorter appointment. The EAG considers the company's original approach to be more appropriate. The EAG also provides a scenario analysis using alternative, lower administration costs, suggested by the company post factual accuracy check (See Table 31 and 32, scenario 12).*

***Health state unit costs and resource use***

Health state costs reflecting resource use for routine monitoring (outpatient appointments, primary care resource use and CT scans) are based on resource use estimates used in prior NICE appraisals TA405 and TA886, are health state-dependent and calculated according to whether the underlying treatment is delivered as an oral or intravenous treatment.[24,29] The company assume patients incur only primary care costs post progression, but an additional one-off terminal care cost (£6,910 in 2022 prices, inflated to £7,748) is applied to all patients to capture the costs of providing palliative care at the end of life.[38]

*The EAG is satisfied that the end-of-life palliative care costs are appropriate and consistent with the reference case perspective of costs. The EAG's clinical expert considered the pre-progression routine monitoring costs to be broadly appropriate, but there was a concern that monitoring appointments for regorafenib may have been underestimated. Given concerns about toxicity with regorafenib in UK clinical practice, additional monitoring in the first two cycles of chemotherapy treatment would likely be required to monitor patients and implement any dose-required adjustments. The company assume a 4-weekly outpatient chemotherapy visit for all oral therapies (trifluridine-tipiracil and regorafenib). However, for regorafenib, the EAG's clinical expert considered weekly appointments in the first 4-weekly cycle of treatment, followed by bi-weekly appointments in the second treatment cycle and 4-weekly thereafter to be more appropriate. These increased monitoring costs are therefore applied for regorafenib in the EAG's preferred base case analysis. Company and EAG's preferred health state costs are summarised in Table 23.*

**Table 23 Company and EAG's preferred resource use assumptions**

| Health state | Treatment | Treatment cycle | The company preferred cost per cycle | EAG's preferred cost per cycle |
|---|---|---|---|---|
| Progression-free | Bevacizumab | All | £66.11 | £66.11 |
| | Trifluridine-tipiracil | All | £63.98 | £63.98 |
| | Regorafenib | 1 (week 0-3) | £63.98 | £211.91 |
| | | 2 (week 4-7) | £63.98 | £113.29 |
| | | 3+ (week 8 +) | £63.98 | £63.98 |
| | BSC | | £1.44 | £13.94 |
| Progressed | All treatments | | £46.06 | £46.06 |

**Key:** BSC, best supportive care; IV, intravenous

***Adverse reaction unit costs and resource use***

Costs for the management of treatment-related Grade 3+ AEs occurring in ≥2% of patients in either arm of the SUNLIGHT study were incorporated into the model based on the incidence reported in Table 22 above. Similarly, to disutilities, a one-off adverse event management cost was calculated and applied in the first model cycle. Total, treatment-specific adverse event costs are summarised in Table 24.

**Table 24 Total adverse event costs**

| Treatment | Cost (£) |
|---|---|
| Trifluridine-tipiracil plus bevacizumab | 668.68 |
| Trifluridine-tipiracil | 670.79 |
| BSC | 64.03 |
| Regorafenib | 625.93 |

**Key:** BSC, best supportive care

*The EAG is satisfied that the company's approach to costing adverse events for the model is generally appropriate. It is noted that the regorafenib AE costs might be expected to be higher for regorafenib, due to the concerns raised about toxicity. However, the EAG's clinical expert has assessed the adverse events reported in the CORRECT study for regorafenib and is satisfied that these are an appropriate representation of the profile of*

*adverse events that would be expected in UK clinical practice. The EAG agrees with the company's estimated total adverse event costs in the model.*

***Subsequent treatments***

For the company's base case model, the proportion of patients receiving subsequent treatments post progression was assumed to be equal across all treatment arms in the model. 58.3% were modelled to require subsequent treatments, based on a pooled estimate across both arms of the SUNLIGHT study (trifluridine-tipiracil + bevacizumab: 61.8%; trifluridine-tipiracil: 55.3%). The same proportion was assumed to apply to those in the regorafenib arm of the model.

*The EAG notes that more effective treatments that prolong progression-free survival might be more likely to be sufficiently fit to receive another line of treatment, however, the differences between the treatment arms of the SUNLIGHT study are small in magnitude and the impact of any biases on the ICER is likely to be minimal given the tendency for OS curves to quickly titrate towards 0%. The EAG is satisfied with the company's approach to using pooled data for the proportion requiring treatment. The approach also maintains consistency with the EAG's preferred approach to applying treatment pooled health state utility values pre- and post-progression.*

Due to the uncertainty of which subsequent treatments patients are likely to receive after their third-line treatment in UK clinical practice, the base case assumes that the same distribution of subsequent treatments is applied to all arms in the model, based on pooled SUNLIGHT data across treatment arms. Details of the distribution of different post-progression treatments included in the model are provided in Table 54 of the company submission. The company explored several scenario analyses, including:

1) removing subsequent treatment costs.
2) applying treatment-specific distributions from SUNLIGHT with an assumption that the distribution for regorafenib is the same as trifluridine-tipiracil monotherapy.
3) applying UK clinical expert opinion which suggested that re-treatment with the same drug post-progression would be rare. It was therefore assumed that trifluridine-tipiracil with or without bevacizumab would receive regorafenib post progression, whereas patients treated with regorafenib at 3rd line, would receive trifluridine-tipiracil monotherapy post progression.

*The EAG notes the advantage of applying post-progression costs that are aligned with the trial data because these are the treatments that may generate overall survival post-progression. However, several of the treatments included in SUNLIGHT for fourth-line therapy are not routinely available or involve combinations of treatments unlikely to be used on the UK NHS. The company's base case also implies that a substantial proportion of regorafenib-treated patients would be re-treated with the same treatment again at 4$^{th}$ line. The company and EAG's clinical expert advisor are in agreement that this would be highly unlikely in UK clinical practice. The EAG prefers the use of subsequent treatment that assumes 58.3% of patients receive treatment post-progression across all arms, and the distribution of post-progression treatment is aligned with the treatments used in UK clinical practice (company scenario 3 above). The EAG noted that the company's preferred unit cost for calcium folinate was obtained from the BNF. However, eMIT prices are available which the EAG considers more appropriate for the purposes of costing given that post-progression treatments will be prescribed and managed from secondary care. The impact on the ICER of implementing this change is small in magnitude and applies only to the company's base case model assumptions. Company and EAG preferred post-progression treatment assumptions and costs are compared in Table 25 below.*

It was further assumed that the duration of treatment post progression was restricted to 2-months. For BSC, no further treatment is expected and, therefore, the cost of subsequent treatment is zero.

*The EAG's clinical expert is satisfied that post-progression treatment would be unlikely to last for longer than 2 cycles of treatment and the company's assumption is therefore reasonable. The EAG is also satisfied that there would be no active chemotherapy following progression for patients treated with best supportive care and the company's assumptions are therefore appropriate.*

**Table 25 Company and EAG's preferred post-progression treatment cost assumptions.**

| Subsequent treatment | Company preferred assumptions | | | EAG's preferred assumptions | | |
|---|---|---|---|---|---|---|
| | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | Regorafenib | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | Regorafenib |
| Proportion treated post-progression | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% | 58.3% |
| **Treatment distribution post-progression:** | | | | | | |
| Regorafenib | 30.9% | 30.9% | 30.9% | 100% | 100% | 0% |
| Capecitabine | 7.6% | 7.6% | 7.6% | 0% | 0% | 0% |
| Doublet chemotherapy | 17.8% | 17.8% | 17.8% | 0% | 0% | 0% |
| Triplet chemotherapy | 4.5% | 4.5% | 4.5% | 0% | 0% | 0% |
| Fruquintinib | 2.6% | 2.6% | 2.6% | 0% | 0% | 0% |
| Trifluridine-tipiracil | 2.3% | 2.3% | 2.3% | 0% | 0% | 100% |
| Irinotecan | 1.9% | 1.9% | 1.9% | 0% | 0% | 0% |
| Nivolumab | 1.5% | 1.5% | 1.5% | 0% | 0% | 0% |
| Bevacizumab+ doublet chemotherapy | 9.4% | 9.4% | 9.4% | 0% | 0% | 0% |
| Bevacizumab + triplet chemotherapy | 2.7% | 2.7% | 2.7% | 0% | 0% | 0% |
| Cetuximab + doublet chemotherapy | 2.3% | 2.3% | 2.3% | 0% | 0% | 0% |
| Cetuximab+ triplet chemotherapy | 1.1% | 1.1% | 1.1% | 0% | 0% | 0% |
| Ramucirumab + doublet chemotherapy | 0.7% | 0.7% | 0.7% | 0% | 0% | 0% |
| Aflibercept + doublet chemotherapy | 1.9% | 1.9% | 1.9% | 0% | 0% | 0% |
| Panitumumab + doublet chemotherapy | 3.4% | 3.4% | 3.4% | 0% | 0% | 0% |
| Capecitabine + oxaliplatin | 8.1% | 8.1% | 8.1% | 0% | 0% | 0% |
| Bevacizumab + capecitabine | 1.1% | 1.1% | 1.1% | 0% | 0% | 0% |
| **Total post-progression treatment acquisition costs** [A] | £3,342.59 | £3,342.59 | £3,342.59 | £4,745.54 | £4,745.54 | £2,110.78 |

[A] Costs excluding any confidential price discounts.

# 5 COST EFFECTIVENESS RESULTS

## *5.1 Company's cost effectiveness results*

The base case results are presented in section B.3.10 of the company submission (document B). The presented results incorporate a simple PAS price discount of [redacted] of Trifluridine-tipiracil. Confidential discounted prices are available for bevacizumab and regorafenib. The impact of these prices on the ICERs is considered by the EAG in a confidential appendix of results.

The intervention technology (trifluridine-tipiracil + bevacizumab) generates higher QALY gains than trifluridine-tipiracil monotherapy, regorafenib or BSC across a wide range of scenario analyses. Life year and QALY gains are accrued primarily in the progression free state, reflecting the PFS benefit seen in the SUNLIGHT study, but the magnitude of life years gained in the post-progression state is sensitive to assumptions about the most appropriate OS curve to fit to the trifluridine-tipiracil +bevacizumab data as well as assumptions about the most appropriate data sources for regorafenib OS and PFS (either based on the NMA, or independently fitted survival curves to the CORRECT study data). Adverse event disutilities are not a major driver of QALY outcomes in the model.

The intervention technology is also more costly than trifluridine-tipiracil monotherapy, regorafenib or BSC, driven primarily by the treatment acquisition costs as well as administration costs for intravenous bevacizumab accrued for a longer time on treatment whilst progression free. Costs of routine monitoring and adverse events are not major drivers of cost-effectiveness results.

Due to the severity of the disease, patients suffering from ≥ 3L mCRC experience a substantial QALY shortfall, compared to the general population. Detailed calculations of company and EAG's preferred QALY shortfall are provided in Chapter 6, but the conclusions are broadly consistent whether the company or EAG scenarios are preferred. The calculated QALY weightings for comparisons against trifluridine-tipiracil is 1.2 (based on a proportional shortfall of 94.84%) and 1.7 for comparisons against regorafenib and BSC (proportional shortfall >95%).

### *5.2 Company's sensitivity analyses*

The company preferred base case deterministic results of pairwise comparisons for trifluridine-tipiracil + bevacizumab compared to each comparator (trifluridine-tipiracil alone, regorafenib, and BSC) are provided in Table 26 and the fully incremental analyses are reported in Table 27 below. Fully incremental analyses rank treatment options in ascending order of costs.

*The EAG notes that the incremental costs and incremental QALYs provided in the company submission are based on exclusion of strictly dominated strategies only. They do not exclude extendedly dominated strategies. However, the ICERs are calculated using a different mechanism and do correctly exclude extendedly dominated strategies from the calculation. Whilst the presented ICERs are correct for decision making, the EAG has reproduced the corrected incremental QALY and incremental cost calculations for completeness in Table 27.*

*The company made some minor changes to their preferred base case in response to clarification queries, applying an updated NMA. The EAG has therefore re-produced all the company's deterministic scenario and probabilistic analyses below, applied to the revised base case post clarification queries.*

*Figures 6 and 7 illustrate the results of the probabilistic analyses with cost-effectiveness acceptability curves and scatter plots of total costs and QALYs for each treatment strategy respectively. Probabilistic analyses reported are for unweighted QALYs. Illustrations applying different severity weightings are available from the company submission.*

**Table 26 Base case and scenario analyses (pairwise comparisons) conducted by the company [reproduced from Tables 5, 8, 9 10 and 18 of the company's clarification response]**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Company preferred base case deterministic analysis post clarification** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Company preferred base case probabilistic analysis post clarification** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | - | 0.62 | [redacted] | - | 0.33 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | - | 0.43 | [redacted] | - | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | - | 0.58 | [redacted] | - | 0.37 | 0.44 | 0.63 | [redacted] | [redacted] | [redacted] |
| **Subgroup results -no prior bevacizumab[A]** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.952 | 1.330 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.951 | 0.624 | [redacted] | 1.001 | 0.707 | 0.848 | 1.201 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.886 | 0.591 | [redacted] | 1.066 | 0.739 | 0.887 | 1.257 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 1.203 | 0.797 | [redacted] | 0.748 | 0.534 | 0.640 | 0.907 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Regorafenib OS and PFS based on generalised gamma survival curves fitted to digitized KM data from the CORRECT study** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.79 | 0.53 | [redacted] | 0.56 | 0.41 | 0.49 | 0.70 | [redacted] | [redacted] | [redacted] |
| **Use OS and PFS HRs obtained from the NMA for both trifluridine-tipiracil monotherapy and regorafenib** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.82 | 0.55 | [redacted] | 0.53 | 0.39 | 0.47 | 0.67 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Regorafenib OS and PFS assumed equal to trifluridine-tipiracil** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Apply chemotherapy treatment administration costs for subsequent treatments using NHS payment scheme prices** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Additional treatment costs for BSC (£13.94 per cycle)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

[A] To implement the subgroup analyses correctly, it is necessary to reset the base case settings in the company's economic model.

**Table 27 Base case and scenario analyses (fully incremental) conducted by the company [reproduced from Tables 6, 7, 19 and the model from the company's clarification response]**

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Company preferred base case deterministic analysis post clarification** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | 0.14 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.52 | [redacted] | [redacted] | [redacted] |
| **Company preferred base case probabilistic analysis post clarification** | | | | | | | |
| BSC | [redacted] | 0.43 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.19 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.58 | [redacted] | 0.15 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.51 | [redacted] | [redacted] | [redacted] |
| **Subgroup results– no prior bevacizumab[A]** | | | | | | | |
| BSC | [redacted] | 0.591 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.624 | [redacted] | 0.033 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.797 | [redacted] | 0.206 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.330 | [redacted] | 0.739 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Regorafenib OS and PFS based on generalised gamma survival curves fitted to digitized KM data from the CORRECT study** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.53 | [redacted] | 0.11 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.52 | [redacted] | [redacted] | [redacted] |
| **Use OS and PFS HRs obtained from the NMA for both trifluridine-tipiracil monotherapy and regorafenib** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.55 | [redacted] | 0.13 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | 0.14 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.52 | [redacted] | [redacted] | [redacted] |
| **Regorafenib OS and PFS assumed equal to trifluridine-tipiracil** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.24 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.62 | [redacted] | 0.24 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.62 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Apply chemotherapy treatment administration costs for subsequent treatments using NHS payment scheme prices** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| FTD/TPI | [redacted] | 0.62 | [redacted] | 0.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | 0.14 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.94 | [redacted] | 0.52 | [redacted] | [redacted] | [redacted] |
| **EAG requested scenario – With additional treatment costs for BSC** | | | | | | | |
| BSC | [redacted] | 0.42 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.62 | [redacted] | 0.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.56 | [redacted] | -0.06 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 0.94 | [redacted] | 0.32 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

[A] To implement the subgroup analyses correctly, it is necessary to reset the base case settings in the company's economic model.

**Figure 6 Company's preferred base case analysis, cost-effectiveness acceptability curve, unweighted QALYs**

**Figure 7 Company's preferred base case analysis, scatter plot of total costs and QALYs, unweighted QALYs**

The company also undertook a range of deterministic one-way sensitivity analyses to test the impact of individual parameter uncertainty on cost-effectiveness results, while

keeping all else as per the base case. Results are illustrated using tornado diagrams (Figures 39-figure 44 of the company submission). The parameters which had the largest impact on results were RDI's for active treatments and HRs for the non-trial comparators.

In addition, a range of further deterministic sensitivity analyses around key modelling assumptions were performed. The results of these analyses are re-produced in Table 28 below, applied to the company's preferred base case analysis post clarification queries.

**Table 28 Deterministic scenario analyses applied to the company preferred base case post clarification.**

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | | ICER versus regorafenib | | | ICER versus BSC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Company preferred base case post clarification** | | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Time horizon | 15 years | 10 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 20 years | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Discount rates | 3.5% | 0.0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | 6.0% | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug wastage | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RDI | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| RDI source for regorafenib | Same as trifluridine/tipiracil | CORRECT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Source for subsequent treatments | SUNLIGHT pooled | No subsequent treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | SUNLIGHT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | UK practice (20% trifluridine-tipiracil+bev; 50% others) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | | ICER versus regorafenib | | | ICER versus BSC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| | | UK practice (40% all) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Age-adjusted disutility | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Utility option | SUNLIGHT - treatment independent | SUNLIGHT - pooled treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | TA866 - Regorafenib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | TA405 - FTD/TPI | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| AE disutility | Included | Excluded | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| OS distribution | Log-logistic | Exponential | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Generalised Gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Gompertz | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Log-logistic | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Log-normal | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Weibull | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PFS distribution | Log-normal | Exponential | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Generalised Gamma | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Gompertz | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | | ICER versus regorafenib | | | ICER versus BSC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| | | Log-logistic | [redacted] | | | | | | | | |
| | | Log-normal | [redacted] | | | | | | | | |
| | | Weibull | [redacted] | | | | | | | | |
| ToT distribution (trifluridine-tipiracil + bevacizumab (trifluridine-tipiracil) | Weibull | Exponential | [redacted] | | | | | | | | |
| | | Generalised Gamma | [redacted] | | | | | | | | |
| | | Gompertz | [redacted] | | | | | | | | |
| | | Log-logistic | [redacted] | | | | | | | | |
| | | Log-normal | [redacted] | | | | | | | | |
| | | Weibull | [redacted] | | | | | | | | |
| ToT distribution (trifluridine-tipiracil + bevacizumab (bevacizumab) | Weibull | Exponential | [redacted] | | | | | | | | |
| | | Generalised Gamma | [redacted] | | | | | | | | |
| | | Gompertz | [redacted] | | | | | | | | |
| | | Log-logistic | [redacted] | | | | | | | | |
| | | Log-normal | [redacted] | | | | | | | | |
| | | Weibull | [redacted] | | | | | | | | |
| ToT distribution | Generalised Gamma | Exponential | [redacted] | | | | | | | | |
| | | Generalised Gamma | [redacted] | | | | | | | | |

| Parameter | Base case | Scenario | ICER versus trifluridine-tipiracil | | | ICER versus regorafenib | | | ICER versus BSC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| (trifluridine-tipiracil) | | Gompertz | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Log-logistic | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Log-normal | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | Weibull | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NMA option | Random effects | Fixed effects | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Regorafenib ToT | Assume same as PFS | Use PFS NMA HR | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Key:** AE, adverse event; BSA, body surface area; BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; ToT, time on treatment

### *5.3 Model validation and face validity check*

The company describe their approach to quality assurance of their model in section B.3. 14 of their submission. The company consulted UK clinical experts to validate the key model assumptions and details of the clinical validation can be found in appendix Q of their submission. The company's model was reported to have been quality assured by an experienced health economist who was not involved in the development of the model.

*The EAG has assessed the model outputs using the checklist by Tappenden and colleagues[39] and conducted several additional face validity checks. The results of the black-box checks are reported in Table 29. The EAG did not identify any further modelling errors and are satisfied that the company's economic model is accurately programmed.*

*In addition, the face validity of the modelled extrapolation curves was discussed with the EAG's clinical expert for the assessment who generally felt that the extrapolations were plausible, but that the OS extrapolations were perhaps an over-estimate of survival. The EAG also inspected the modelled outputs, mean and median time on treatment and progression free survival for regorafenib against the available data from the CORRECT study, finding that modelled time on treatment over-estimated reported data. These issues are explored in scenario analyses in Chapter 6.*

**Table 29 Model face validity check**

| Model component | Model test | Unequivocal criterion for verification | Issues identified in company model |
|---|---|---|---|
| Clinical trajectory | Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events) | All treatments produce equal estimates of total LYGs and total QALYs | The QALYs LYGs are equivalent across treatment arms when the model is run using the OS and PFS HRs obtained from the NMA (set to 1), treatment specific HSUVs are removed, and adverse event disutilities are removed. |
| | Sum expected health state populations at any model timepoint (state transition models) | Total probability equals 1.0 | No issues identified. |
| QALY estimation | Set all health utility for living states parameters to 1.0 | QALY gains equal LYGs | No issues identified. |
| | Set QALY discount rate to 0 | Discounted QALYs = undiscounted QALYs for all treatments | No issues identified. |
| | Set QALY discount rate equal to very large number | QALY gain after time 0 tend towards zero | No issues identified |

| Model component | Model test | Unequivocal criterion for verification | Issues identified in company model |
|---|---|---|---|
| Cost estimation | Set intervention costs to 0 | ICER is reduced | No issues identified |
| | Increase intervention cost | ICER is increased | No issues identified |
| | Set cost discount rate to 0 | Discounted costs = undiscounted costs for all treatments | No issues identified |
| | Set cost discount rate equal to very large number | Costs after time 0 tend towards zero | No issues identified |
| Input parameters | Produce n samples of model parameter m | Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter. | No issues detected |
| General | Set all treatment-specific parameters equal for all treatment groups | Costs and QALYs equal for all treatments | No issues identified. Equalized survival curves led to equal LYs and QALYs. Treatment costs are more challenging to equalize as they are based on different dosing schedules and pack sizes. |
| | Amend value of each individual model parameter | ICER is changed | No issues identified. The parameters amended changed the ICER and the direction of impact on ICERs was as expected. |

| Model component | Model test | Unequivocal criterion for verification | Issues identified in company model |
|---|---|---|---|
| | Switch all treatment-specific parameter values | QALYs and costs for each option should be switched | Given the complexity of the model structure and calculations, this was difficult to complete fully, however no issues were identified. |

**Key:** HR, hazard ratio; HSUV, health state utility values; ICER, incremental cost-effectiveness ratio; LYGs, life years gained; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life years.

# 6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

## *6.1 Exploratory and sensitivity analyses undertaken by the EAG.*

The EAG undertook several scenario analyses to address issues and uncertainties identified in chapter 4. Adaptations to the company's economic model included:

1) Calculating incremental costs and QALYs for reported results tables based on exclusion of both extendedly and strictly dominated strategies. This amendment has no impact on the ICER.
2) Exploring alternative assumptions for regorafenib time on treatment
3) Applying additional monitoring costs for regorafenib
4) Applying a minor costing change to source post-progression treatment costs for calcium folinate from eMIT rather than drug tariff prices from the BNF.

Full justification for all EAG conducted scenarios is incorporated into table 30 below.

## *6.2 Impact on the ICER of additional economic analyses undertaken by the EAG and preferred assumptions.*

The results of EAG conducted analyses are provided in Tables 31 and 32 for the fully incremental and pairwise comparisons respectively. Probabilistic results and the impact of the company conducted subgroup analysis for no prior bevacizumab on the EAG's preferred base case are also reported.

**Table 30 Description and justification of EAG's preferred scenario analyses**

| Scenario number | Parameter or assumption | Company base case | EAG scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 1 | Trifluridine Tipiracil +bevacizumab and Trifluridine tipiracil OS | Apply log-logistic curve | Apply generalised gamma curve | Generalised gamma predicts 5-year OS of <1% in line with EAG expert opinion and maintains an extrapolated effect size that up to 2 years that is more consistent with the KM data. | 4.2.6 |
| 2 | OS and PFS curves for Regorafenib | HR from random-effects NMA applied to trifluridine-tipiracil + bevacizumab curve | Independently fitted using data from the CORRECT study | Applying a hazard ratio directly to an accelerated failure time model may over or underestimate OS and PFS at different points on the curve. The EAG's clinical expert considered the SUNLIGHT and CORRECT study populations to be sufficiently comparable to allow a naïve comparison between studies and fit OS and PFS curves independently to the CORRECT trial data for regorafenib. | 4.2.6 |
| 3 | ToT for Regorafenib | Assume ToT is equal to PFS | Proportion on treatment in each cycle | The company preferred approach assumes treatment to the point of progression. However, clinical expert opinion is that regorafenib may be discontinued early | 4.2.6 |

| Scenario number | Parameter or assumption | Company base case | EAG scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| | | | calculated as PFS x (mean CORRECT ToT / Mean modelled PFS) | due to toxicity. Similarly, median PFS and ToT from the CORRECT study are not equal. The EAG's approach leads to modelled median and mean ToT that more accurately represents the CORRECT study data. | |
| 4 | Health state utility values | Treatment dependent | Treatment pooled | The EAG does not consider the company's justification to be sufficiently robust to support treatment specific HSUVs. Treatment specific HSUVs are not supported by mixed-effects regression models that adjust for baseline utility. Justification based on supporting clinical data are not provided specifically for progression free patients and the clinical expert opinion does not support treatment specific values, particularly in the post progression state. | 4.2.7 |
| 5 | Regorafenib RDI | Assumed equal to trifluridine-tipiracil | Use data from the CORRECT study | The EAG's approach more accurately reflects the treatment specific RDI and maintains consistency with the EAG's preferred data source for OS, PFS and ToT | 4.2.8 |

| Scenario number | Parameter or assumption | Company base case | EAG scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 6 | Regorafenib monitoring costs | Monthly outpatient monitoring visits (similar to trifluridine-tipiracil) | Additional monitoring costs for Regorafenib (Weekly for chemo cycle 1; bi-weekly for chemo cycle 2 and monthly thereafter) | The EAG and the company clinical expert opinion both suggested that regorafenib may be associated with additional toxicity. The EAG's expert was of the view that more intensive monitoring of regorafenib patients would be required in UK clinical practice. The EAG therefore prefer additional monitoring costs for regorafenib | 4.2.8 |
| 7 | Best supportive care costs | £1.44 | £13.94 per cycle | The EAG considers the company scenario analysis that provides some resource use as per TA866. | 4.2.8 |
| 8 | Treatment acquisition costs for calcium folinate post progression treatment | Apply drug tariff prices obtained from the BNF | Apply eMIT prices | The EAG prefers the use of eMIT prices because they more accurately reflect the costs of prescribing in secondary care. | 4.2.8 |

| Scenario number | Parameter or assumption | Company base case | EAG scenario | Justification | Section of EAG report |
|---|---|---|---|---|---|
| 9 | Post progression treatment costs | Proportion requiring treatment & treatment distribution from pooled SUNLIGHT data. | Proportion requiring treatment as per company. Treatment distribution (trifluridine-tipiracil get regorafenib; regorafenib get trifluridine-tipiracil) | The company distribution of post-progression treatments includes treatments not routinely available in UK clinical practice and combinations of chemotherapy that would not usually be used at 4th line. The EAG's approach more accurately reflects UK clinical practice, but the EAG notes that the distribution of post-progression treatments is not a major driver of cost-effectiveness | 4.2.8 |
| **10** | **EAG preferred base case** | **N/A** | **Scenarios 1-9 combined** | | |

**Key:** NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; RDI, relative dose intensity; TA, technology appraisal; ToT, time on treatment.

**Table 31 EAG's preferred analyses - fully incremental (with PAS), all severity modifiers (no weight, x1.2 and x1.7)**

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Company preferred base case post clarification queries** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 1: Generalised Gamma OS curves for Trifluridine Tipiracil +bevacizumab and Trifluridine tipiracil** | | | | | | | |
| BSC | [redacted] | 0.418 | | | | | |
| FTD/TPI | [redacted] | 0.591 | [redacted] | 0.173 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.537 | [redacted] | -0.054 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.811 | [redacted] | 0.220 | [redacted] | [redacted] | [redacted] |
| **Scenario 2: Independently fitted OS and PFS curves for Regorafenib (Using CORRECT study data)[18]** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.529 | [redacted] | 0.108 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 3: ToT for Regorafenib: Apply ratio of mean ToT from CORRECT study / Mean modelled PFS (67.6% of progression-free patients remaining on Regorafenib treatment when applied to company base case)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 4: Apply pooled HSUVs** | | | | | | | |
| BSC | [redacted] | 0.435 | | | | | |
| FTD/TPI | [redacted] | 0.637 | [redacted] | 0.202 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.576 | [redacted] | -0.061 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.914 | [redacted] | 0.277 | [redacted] | [redacted] | [redacted] |
| **Scenario 5: Apply EAG preferred relative dose intensity for regorafenib (CORRECT study)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 6: Apply additional monitoring costs for Regorafenib (Weekly for chemo cycle 1; bi-weekly for chemo cycle 2 and monthly thereafter)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 7: Apply additional BSC costs (£13.94 per cycle)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | -0.059 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.324 | [redacted] | [redacted] | [redacted] |
| **Scenario 8: Apply eMIT costs for calcium folinate post progression treatment** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | -0.059 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.324 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 9: Apply EAG preferred post progression costs (58.3% receive treatment; distribution: regorafenib post trifluridine-tipiracil + bevacizumab & trifluridine-tipiracil alone; trifluridine-tipiracil post regorafenib)** | | | | | | | |
| BSC | [redacted] | 0.422 | | | | | |
| FTD/TPI | [redacted] | 0.617 | [redacted] | 0.196 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.558 | [redacted] | 0.137 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.941 | [redacted] | 0.520 | [redacted] | [redacted] | [redacted] |
| **Scenario 10: EAG preferred base case analysis (Scenarios 1-9 combined) - Deterministic** | | | | | | | |
| BSC | [redacted] | 0.431 | | | | | |
| FTD/TPI | [redacted] | 0.609 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.546 | [redacted] | -0.063 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.788 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| **Scenario 11: 10 + Alternative EAG scenario analysis, calculating regorafenib ToT using median from CORRECT, fitting an exponential distribution** | | | | | | | |
| BSC | [redacted] | 0.431 | | | | | |
| FTD/TPI | [redacted] | 0.609 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.546 | [redacted] | -0.063 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.788 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 12: 10 + Alternative treatment administration costs for treatments administered as IV, apply HRG SB12Z, £188.06 for day 1, and SB15Z, £186.56 for day 15 of each 28-day cycle.** | | | | | | | |
| BSC | [redacted] | 0.431 | | | | | |
| FTD/TPI | [redacted] | 0.609 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.546 | [redacted] | -0.063 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.788 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-9 combined) - Probabilistic** | | | | | | | |
| BSC | [redacted] | 0.435 | | | | | |
| FTD/TPI | [redacted] | 0.627 | [redacted] | 0.191 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.559 | [redacted] | -0.067 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.800 | [redacted] | 0.173 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Table 32 EAG's preferred analyses - pairwise comparisons (with PAS), all severity modifiers (x1.0, x1.2 and x1.7)**

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Company preferred base case post clarification queries** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |
| **Scenario 1: Generalised Gamma OS curves for Trifluridine Tipiracil +bevacizumab and Trifluridine tipiracil** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.125 | 0.811 | | | | | | | | |
| FTD/TPI | [redacted] | 0.893 | 0.591 | [redacted] | 0.232 | 0.220 | 0.264 | 0.374 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.620 | 0.418 | [redacted] | 0.505 | 0.393 | 0.471 | 0.668 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.793 | 0.537 | [redacted] | 0.332 | 0.274 | 0.329 | 0.466 | [redacted] | [redacted] | [redacted] |
| **Scenario 2: Independently fitted OS and PFS curves for Regorafenib (Using CORRECT study data)**[18] | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.793 | 0.529 | [redacted] | 0.560 | 0.412 | 0.494 | 0.700 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Scenario 3: ToT for Regorafenib: Apply ratio of mean ToT from CORRECT study / Mean modelled PFS (67.6% of progression-free patients remaining on regorafenib treatment when applied to company base case)[18]** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |
| **Scenario 4: Apply pooled HSUVs** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.914 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.637 | [redacted] | 0.406 | 0.277 | 0.333 | 0.471 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.435 | [redacted] | 0.726 | 0.479 | 0.575 | 0.815 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.576 | [redacted] | 0.523 | 0.339 | 0.406 | 0.576 | [redacted] | [redacted] | [redacted] |
| **Scenario 5: Apply EAG preferred relative dose intensity for regorafenib (CORRECT study[18])** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Scenario 6: Apply additional monitoring costs for Regorafenib (Weekly for chemo cycle 1; bi-weekly for chemo cycle 2 and monthly thereafter)** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |
| **Scenario 7: Apply additional BSC costs (£13.94 per cycle)** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |
| **Scenario 8: Apply eMIT costs for calcium folinate post progression treatment** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Scenario 9: Apply EAG preferred post progression costs (58.3% receive treatment; distribution: regorafenib post trifluridine-tipiracil + bevacizumab & trifluridine-tipiracil alone; trifluridine-tipiracil post regorafenib)** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.353 | 0.941 | | | | | | | | |
| FTD/TPI | [redacted] | 0.947 | 0.617 | [redacted] | 0.406 | 0.324 | 0.388 | 0.550 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.626 | 0.422 | [redacted] | 0.726 | 0.520 | 0.623 | 0.883 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.830 | 0.558 | [redacted] | 0.523 | 0.383 | 0.460 | 0.651 | [redacted] | [redacted] | [redacted] |
| **Scenario 10: EAG preferred base case analysis (Scenarios 1-9 combined) - Deterministic** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.125 | 0.788 | | | | | | | | |
| FTD/TPI | [redacted] | 0.893 | 0.609 | [redacted] | 0.232 | 0.178 | 0.214 | 0.303 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.620 | 0.431 | [redacted] | 0.505 | 0.357 | 0.428 | 0.606 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.793 | 0.546 | [redacted] | 0.332 | 0.242 | 0.290 | 0.411 | [redacted] | [redacted] | [redacted] |
| **Scenario 11: 10 + Alternative EAG scenario analysis, calculating regorafenib ToT using median from CORRECT, fitting an exponential distribution** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.13 | 0.79 | | | | | | | | |
| FTD/TPI | [redacted] | 0.89 | 0.61 | [redacted] | 0.23 | 0.18 | 0.21 | 0.30 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.62 | 0.43 | [redacted] | 0.50 | 0.36 | 0.43 | 0.61 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.79 | 0.55 | [redacted] | 0.33 | 0.24 | 0.29 | 0.41 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Scenario 12: 10 + Alternative treatment administration costs for treatments administered as IV, apply HRG SB12Z, £188.06 for day 1, and SB15Z, £186.56 for day 15 of each 28-day cycle.** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.13 | 0.79 | | | | | | | | |
| FTD/TPI | [redacted] | 0.89 | 0.61 | [redacted] | 0.23 | 0.18 | 0.21 | 0.30 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.62 | 0.43 | [redacted] | 0.50 | 0.36 | 0.43 | 0.61 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.79 | 0.55 | [redacted] | 0.33 | 0.24 | 0.29 | 0.41 | [redacted] | [redacted] | [redacted] |
| **EAG preferred base case analysis (Scenarios 1-9 combined) - Probabilistic** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | -- | 0.800 | | | | | | | | |
| FTD/TPI | [redacted] | -- | 0.627 | [redacted] | -- | 0.173 | 0.208 | 0.295 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | -- | 0.435 | [redacted] | -- | 0.365 | 0.438 | 0.620 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | -- | 0.559 | [redacted] | -- | 0.241 | 0.289 | 0.410 | [redacted] | [redacted] | [redacted] |

**Key:** BSC, best supportive care; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

**Figure 8 EAG's preferred base case analysis, cost-effectiveness acceptability curve, unweighted QALYs.**

**Figure 9 EAG's preferred base case analysis, scatter plot of total costs and QALYs, unweighted QALYs.**

### *6.3 Conclusions of the cost-effectiveness section*

Interpretation of the cost-effectiveness results requires a judgement call on the most appropriate severity weighting to be applied. Both the company and EAG's preferred base case analyses are similar, resulting in a 1.2 weighting for trifluridine-tipiracil and a 1.7 weighting for regorafenib. The detailed calculations for the company and EAG preferred base case analyses are compared in Table 33 below. Probabilistic analyses generate similar results.

**Table 33 QALY shortfall calculations (company versus EAG's preferred scenarios)**

| Remaining QALYs | Trifluridine-tipiracil + bevacizumab | Trifluridine-tipiracil | Regorafenib | BSC |
|---|---|---|---|---|
| **Company preferred base case results (Deterministic)** | | | | |
| Without disease | 12.01 | 12.01 | 12.01 | 12.01 |
| With Disease | 0.94 | 0.62 | 0.56 | 0.42 |
| Absolute shortfall | 11.07 | 11.39 | 11.45 | 11.59 |
| Proportional shortfall | 92.17% | 94.84% | 95.34% | 96.50% |
| QALY weight | | x1.2 | x1.7 | x1.7 |
| **EAG preferred base case results (Deterministic)** | | | | |
| Without disease | 12.01 | 12.01 | 12.01 | 12.01 |
| With Disease | 0.79 | 0.61 | 0.55 | 0.43 |
| Absolute shortfall | 11.22 | 11.4 | 11.46 | 11.58 |
| Proportional shortfall | 93.42% | 94.92% | 95.42% | 96.42% |
| QALY weight | | x1.2 | x1.7 | x1.7 |

**Key:** BSC, best supportive care; QALY, quality-adjusted life year

Applying the appropriate QALY severity weightings leads pairwise ICERs for trifluridine-tipiracil + bevacizumab in the company's base case analysis of [redacted] vs. trifluridine-tipiracil monotherapy, [redacted] vs. BSC, and [redacted] vs. regorafenib. Under the EAG's preferred set of assumptions, the corresponding ICERs for trifluridine-tipiracil + bevacizumab are [redacted] vs. trifluridine-tipiracil monotherapy, [redacted] vs. BSC and [redacted] vs. regorafenib. Cost-effectiveness conclusions will also depend on the consideration of confidential prices for bevacizumab, comparators, and

subsequent post-progression treatments. Analyses are reproduced using these prices in a confidential appendix.

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# Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

# [redacted]ADDENDUM TO THE EAG REPORT


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**Strictly confidential: Contains [redacted] information**

## Overview

This addendum should be read in conjunction with the EAG report (v2.0 post Factual accuracy check) for the NICE technology appraisal of Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]. The purpose of this addendum is to provide additional critique of the company's subgroup economic model analyses for patients with no prior bevacizumab and to update the EAG report with a scenario analysis, applied to the EAG preferred base case, that considers the impact of this subgroup on cost-effectiveness results. Tables 1 and 2 in this document are intended to provide an additional scenario (Scenario number 13) to Tables 31 and 32 of the EAG report.

## Critique of the subgroup analyses

The EAG note that neither the company, nor the EAG consider the subgroup analysis of patients from the SUNLIGHT trial with 'no prior bevacizumab' as the basis for the base case economic model. The EAG considers the company's chosen approach of using the full ITT population from the SUNLIGHT trial to populate the economic model to be appropriate for decision making, despite a lack of bevacizumab availability in UK clinical practice. The approach to parameterising the subgroup analysis of 'no prior bevacizumab', based on SUNLIGHT trial data, is described in detail in Appendix M of the company submission.

*The company assessed a range of parametric survival models for OS, PFS and ToT. Overall, the company's methodology for selecting curves appears appropriate, but the EAG disagrees with the chosen overall survival curves on clinical plausibility grounds. For all subgroup analyses, the EAG cautions that analyses are likely to be subject to increased uncertainty, driven by the smaller sample of data available for this subgroup from the SUNLIGHT trial. Whilst the company have not provided details of the sample available for survival modelling in the subgroup, the EAG note that only 28% of the SUNLIGHT trial participants had 'no previous bevacizumab' at baseline (N=138, trifluridine-tipiracil + bevacizumab: N=68 ; trifluridine-tipiracil: N=70).*

*Despite the EAG's preference to consider the full ITT population for decision making, the following is a brief critique and analysis should the committee wish to consider the subgroup analyses in decision making.*

***Overall survival***

For OS, the company chose a log-normal curve for both trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil. This was justified on the grounds of good statistical fit of the curves and company expert assessed clinical plausibility of the extrapolations.

*The EAG note that the chosen OS curve, particularly for trifluridine-tipiracil + bevacizumab has a substantial impact on LYGs and the estimates of the ICER. This can be seen in Figure 7 of Appendix M of the company submission. The company note that, with the exception of the exponential curve, most extrapolations fit the data reasonably well in terms of AIC and BIC. The EAG agree and note that the most appropriate extrapolation curve relies on the plausibility of the longer-term 2 and 5-year survival proportions. The company chose a log-normal curve for both trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil, whereas the EAG prefers a Weibull curve for trifluridine-tipiracil + bevacizumab, on the grounds that the Weibull curve predicts lower proportions alive at 5 years. The EAG's clinical expert view is that few if any participants will remain alive at 5 years, regardless of treatment arm. The company also note in Appendix M that clinical experts consulted by the company considered the chosen log-normal curve to provide survival estimates that were higher than expected. For these reasons, the EAG prefers the Weibull as the most appropriate curve to estimate OS for trifluridine-tipiracil + bevacizumab. Given that comparable subgroup data are not available for regorafenib, the EAG has chosen to apply HRs for the remaining comparators to avoid counter-intuitive results. Company and EAG preferred OS extrapolations for the 'no prior bevacizumab' subgroup are provided in Table 1 below:*

**Table 1: Comparison of company and EAG preferred trifluridine-tipiracil + bevacizumab OS curves for no prior bevacizumab subgroup**

| | **Company preferred – Log-Normal** | **EAG preferred - Weibull** |
|---|---|---|
| | **Trifluridine-tipiracil + bevacizumab** | **Trifluridine-tipiracil + bevacizumab** |
| **AIC** | 248.1 | 247.5 |
| **BIC** | 252.5 | 251.9 |
| **Proportion alive at 1 year** | 62% | 63% |
| **Proportion alive at 2 years** | 32% | 21% |
| **Proportion alive at 5 years** | 7% | 0% |
| **Proportion alive at 10 years** | 1% | 0% |

***Progression free survival***

Based on assessment of statistical fit (AIC and BIC), and clinical expert opinion, the company also chose a log-normal curve to model PFS for both arms.

*The EAG agrees that there is little difference in statistical fit between the curves. However, the EAG notes that applying a log-normal curve for PFS and Weibull curve for OS (as per EAG preference above) generates results that allow PFS and OS curves to converge over time. Given that the Weibull survival curve is also a good fit to the data, the EAG also prefers to use the Weibull for PFS for trifluridine-tipiracil + bevacizumab to ensure more plausible extrapolation outcomes. As for OS, the HRs from the NMA are applied for trifluridine-tipiracil alone to ensure face validity. The company and EAG preferred PFS assumptions are tabulated in Table 2 below.*

**Table 2: Comparison of company and EAG preferred PFS curves for no prior bevacizumab subgroup**

| | Company preferred - Trifluridine-tipiracil + bevacizumab | EAG preferred - Trifluridine-tipiracil + bevacizumab |
|---|---|---|
| **AIC** | 332.2 | 328.9 |
| **BIC** | 336.7 | 333.3 |
| **Proportion progression free at 1 year** | 26% | 23% |
| **Proportion progression free at 2 years** | 7% | 1% |
| **Proportion progression free at 5 years** | 0% | 0% |
| **Proportion progression free at 10 years** | 0% | 0% |

***Time on treatment***

For trifluridine-tipiracil + bevacizumab, a Weibull is selected based on plausibility of outputs, and reasonable fit to the underlying data. For trifluridine-tipiracil, a log-normal is chosen.

*The EAG considers the company's decisions to be reasonable.*

***Summary***

The EAG has several concerns regarding the appropriateness of the company presented subgroup model analyses, as follows:

1) The company's estimates of overall survival in the trifluridine-tipiracil + bevacizumab group are overly optimistic, and the EAG prefers a more conservative Weibull curve, which implies all patients have died by 5 years.
2) Subgroup analyses are based on limited data and are thus highly uncertain.
3) Comparisons vs. regorafenib and BSC should be interpreted particularly cautiously given that similar subgroup data are not available for those treatments. The company has assumed that the HRs derived from the NMA for the full ITT populations across all included studies are transferrable to the subgroup population, but it is unclear whether these assumptions are supported by evidence. It should also be noted that the EAG's critique in the main report relates to the ITT population cost-effectiveness model. Some scenarios applied to the ITT population may be inappropriate for the 'no prior bevacizumab' subgroup. For example, using NMA HRs for BSC, but independently fitted curves for PFS and OS for regorafenib generate results that lack face validity (i.e. BSC superior to regorafenib). Therefore, the EAG preferred base case for the subgroup analysis applies the OS and PFS NMA HR results for all treatments compared to trifluridine-tipiracil + bevacizumab. However, these HRs are derived from the full ITT populations from the respective trials and may not accurately reflect HRs if it was possible to conduct an NMA using data from the subgroup population only. It should also be noted that the EAG does not have access to independently fitted curves for the BSC arm of the CORRECT study but would be happy to consider these should the company wish to provide them.
4) Additionally, the company assume that HSUVs are the same in both the ITT and 'no prior bevacizumab' groups. Whilst this may be a reasonable assumption, the EAG notes that the results have not been explored in the subgroup and there may be differences in utility across subgroups that have not been identified.

Due to these concerns the EAG are strongly of the view that the subgroup analyses should be considered as exploratory only and should not form the basis of decision making. Particular caution is required when combining some of the EAG preferred assumptions, based on an ITT population, with the subgroup population. Despite the concerns raised, clinical effectiveness subgroup data appear to show greater benefit in the 'no prior bevacizumab' subgroup, and this may indicate that the company and EAG cost-effectiveness estimates are conservative, given the lack of prior bevacizumab treatment in UK clinical practice.

Table 3 below compares the company and EAG preferred base case assumptions when applied to the 'no prior bevacizumab' subgroup population. As described above, in several cases these assumptions differ to those applied in the full population to ensure plausibility of outcomes. For comparison against EAG preferred assumptions for the full ITT population, please see Table 30 of the EAG report. Results of the EAG preferred subgroup analysis are provided in Tables 4 and 5 for a fully incremental and pairwise analysis respectively. Should committee wish to consider the subgroup analysis for decision making, it should be noted that, using the company's preferred assumptions, QALY shortfall analysis suggests that multipliers of 1.2, 1.2 and 1.7 should be applied for trifluridine-tipiracil, regorafenib and BSC respectively.

**Table 3 EAG preferred assumptions for ITT and no prior bevacizumab subgroups**

| Assumption | No Prior Bevacizumab | |
|---|---|---|
| | **Company** | **EAG** |
| **Trifluridine-tipiracil + bevacizumab OS & PFS curves** | Log-Normal curve | Weibull curve |
| **Regorafenib and trifluridine-tipiracil OS and PFS** | HRs from NMA | HRs from NMA |
| **ToT for regorafenib** | Assume ToT equal to PFS | Apply a proportion of the PFS curve on treatment |
| **HSUVs** | Treatment dependent | Treatment pooled |
| **Regorafenib RDI** | Equal to trifluridine-tipiracil | Use data from CORRECT study |
| **Regorafenib monitoring costs** | Monthly outpatient | Additional monitoring |
| **BSC** | £1.44 | £13.94 per cycle |
| **Calcium folinate costs** | Drug tariff price | eMIT price |
| **Post progression treatments** | Trial based | User input (only regorafenib and trifluridine-tipiracil considered post progression) |

**Table 4 EAG base case analysis for full ITT population (EAG base case) and no prior bevacizumab subgroup (Adds an additional scenario to Table 31 of the EAG report – fully incremental analyses).**

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x 1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Scenario 10 – EAG preferred base case analysis.** | | | | | | | |
| BSC | [redacted] | 0.431 | | | | | |
| FTD/TPI | [redacted] | 0.609 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.546 | [redacted] | -0.063 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.788 | [redacted] | 0.178 | [redacted] | [redacted] | [redacted] |
| **Scenario 13: 10 + Subgroup – no prior bevacizumab (apply PFS and OS NMA for trifluridine-tipiracil, and regorafenib) [A]** | | | | | | | |
| BSC | [redacted] | 0.583 | | | | | |
| FTD/TPI | [redacted] | 0.715 | [redacted] | 0.132 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.726 | [redacted] | 0.143 | [redacted] | [redacted] | [redacted] |
| FTD/TPI + bevacizumab | [redacted] | 0.967 | [redacted] | 0.384 | [redacted] | [redacted] | [redacted] |

**Table 5 EAG base case analysis for full ITT population (EAG base case) and no prior bevacizumab subgroup (Adds an additional scenario to Table 32 of the EAG report – pairwise comparison analyses).**

| Technologies | Total | | | Incremental | | | | | ICER, (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYs | QALYs | Costs (£) | LYs | QALYs (x1) | QALYs (x1.2) | QALYs (x1.7) | x1.0 | x1.2 | x1.7 |
| **Scenario 10: EAG preferred base case analysis (Scenarios 1-9 combined) - Deterministic** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.125 | 0.788 | | | | | | | | |
| FTD/TPI | [redacted] | 0.893 | 0.609 | [redacted] | 0.232 | 0.178 | 0.214 | 0.303 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.620 | 0.431 | [redacted] | 0.505 | 0.357 | 0.428 | 0.606 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.793 | 0.546 | [redacted] | 0.332 | 0.242 | 0.290 | 0.411 | [redacted] | [redacted] | [redacted] |
| **Scenario 13: 10 + Subgroup – no prior bevacizumab (apply PFS and OS NMA for trifluridine-tipiracil, and regorafenib) [A]** | | | | | | | | | | | |
| FTD/TPI + bevacizumab | [redacted] | 1.391 | 0.967 | | | | | | | | |
| FTD/TPI | [redacted] | 1.032 | 0.715 | [redacted] | 0.359 | 0.252 | 0.302 | 0.428 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.840 | 0.583 | [redacted] | 0.551 | 0.384 | 0.461 | 0.653 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 1.042 | 0.726 | [redacted] | 0.349 | 0.241 | 0.289 | 0.409 | [redacted] | [redacted] | [redacted] |

[A] **Note**: Independently fitted data were not provided to the EAG for BSC.

**Single Technology Appraisal**

**Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **5 March 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

**Issue 1 Efficacy**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 36: "*It is therefore unclear, for example why the generalised gamma was not considered as an appropriate option at this stage as it has very similar, and in some cases slightly better AIC and BIC scores than log-logistic / log-normal as demonstrated in Table 15 above.*"<br><br>This statement is mis-leading as there is only one instance of the AIC being better for the trifluridine-tipiracil monotherapy. In other cases the generalised gamma is statistically 'worse' than log-logistic.<br><br>The company also consider their description of the curve choices to be clear, highlighting log-logistic and log-normal as statistically the best fitting and describing similar AIC/BIC of others after excluding exponential and Gompertz. Generalised gamma was only mentioned by one clinician in regards to trifluridine-tipiracil monotherapy in addition to log-logistic and was also never mentioned by the clinicians in relation to trifluridine-tipiracil plus bevacizumab and therefore did not need to be specifically called out for consideration. | The company request this statement to be removed from the EAG report. | This statement is misleading in the appropriateness of generalised gamma in terms of statistical fit and leads the reader to believe the company did not provide adequate evidence to consider it in their base case decision. | This is not a factual inaccuracy.<br><br>The EAG report clearly states on page 33 that the company's general approach to assessment of survival curves is appropriate and aligned with best practice methods.<br><br>The EAG critique clearly states that "*all the curves, except Gompertz and exponential to be approximately equivalent in terms of visual and statistical fit*"<br><br>The EAG select the generalised gamma as the preferred curve, primarily due to the predicted proportion alive at 5 years, which, in the EAG's clinical expert opinion is an overestimate compared to |

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| | | | what might be expected in UK clinical practice.<br><br>To avoid any misinterpretation, the EAG has amended the statement to:<br><br>*"…and in the case of trifluridine monotherapy, has a slightly better AIC compared to the log-logistic curve…*" |
| Page 36: "*However, the selection of curves based on expert opinion introduces uncertainty, particularly for the new intervention treatment as there is little experience with its use in a real-world setting."*<br><br>"*The EAG clinical expert is of the view that almost no patients will remain alive at 5 years, regardless of treatment arm and any treatment benefits would be observed at the start of the extrapolation phase."*<br><br>The EAG statements are contradictory as they state that using clinical expert opinion introduces uncertainty in the intervention arm whilst choosing their base case curve based on one clinical expert opinion of long-term projections versus the company's six clinical experts. Each of the company's clinical | The EAG should amend their description to highlight the uncertainty in their choice of curve based on one clinical expert. | The statements are contradictory. | This is not a factual inaccuracy, but a difference of opinion amongst clinical experts.<br><br>The EAG retains the view that the most appropriate choice of OS extrapolation curve is uncertain. Given the absence of long-term follow up data, or real-world evidence presented by the company, it is necessary to rely on clinical expert opinion about the most clinically plausible long-term extrapolations.<br><br>The advice sought from both the company and EAG |

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| expert was interviewed individually and therefore not influenced by each other's responses. | | | are uncertain, particularly for the new intervention, with which there is limited experience in UK clinical practice.<br><br>The EAG's clinical expert further clarifies that, whilst up to 5% of patients with a diagnosis of metCRC who do not receive salvage surgery will still be alive at 5 years, that is not their view of the type of patient going into 3rd line Lonsurf (+/- bevacizumab) in daily practice, where outcomes are likely to be substantially worse.<br><br>The EAG and company preferred base case analyses represent differences of clinical expert opinion, and therefore this is not a factual inaccuracy.<br><br>No amendments required. |
| Page 42: "*Given a lack of alternative data, the EAG considers the approach of applying the HR from the NMA for BSC to be* | The EAG should amend the statement to clarify why different approaches to the comparators is | The statement is not factually accurate regarding the BSC data availability | The sentence has been reworded to note that the digitised data for BSC were not requested by the EAG, or provided in any of the |

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| *appropriate for decision making, despite the highlighted limitations."*<br><br>This statement is not true as there is a placebo arm in the CORRECT study, however this was never requested by the EAG at clarification stage. Therefore it is unclear why the EAG feel this approach is appropriate for BSC but not regorafenib. | preferred over the company's base case | | company submitted documentation.<br><br>Should the company wish to provide an analysis fitting independent curves to the BSC data, the EAG would be happy to consider this prior to the appraisal committee meeting. |

**Issue 2 Duration of treatment**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
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| Page 46 – 48.<br><br>The EAG's approach to estimate ToT for regorafenib is to apply a percentage to the PFS curve implying that only a fixed proportion of patients who are progression-free are on treatment. Although the company can see the EAG's rationale for this assumption, there are serious concerns with the face validity of this approach. This can be seen in Figure 5 of the EAG report which shows the EAG's curve starting at 80%: | The company provided an alternative scenario to estimate regorafenib ToT using the PFS NMA HR. If the EAG consider a need to explore alternative scenarios, then using another HR approach (e.g., estimating the HR between PFS and ToT of trifluridine-tipiracil monotherapy), or extrapolating the CORRECT ToT median or mean using an exponential distribution would produce more plausible ToT curves. | The resulting ToT curves are implausible and underestimate the regorafenib drug acquisition costs particularly in the first cycle. This approach assumes that in cycle 0 only 80% of patients receive regorafenib. | The EAG maintains our preferred base case assumption as it provides good face validity when compared against the median and mean ToT data available in the public domain for regorafenib. The EAG therefore does not believe that the approach taken underestimates total treatment acquisition costs for regorafenib. |

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|  <br>This implies that at baseline, whilst 100% of patients are progression-free, only 80% receive treatment in cycle 1 (this reduces to 67% using the company's base case curves). This is in addition to the RDI applied which covers dose modifications and interruptions due to AEs. This underestimates the regorafenib drug acquisition costs and seems an implausible assumption given patients wouldn't stop treatment for adverse events before progression if they have never received treatment. | | | The EAG does however appreciate the company's alternative suggestions and we have added an additional scenario analysis in Chapter 6, using median ToT from the CORRECT trial (7.39 weeks), and applying an exponential distribution. The results can be found as scenario 11 in Tables 31 and 32 of the EAG report post FAC and the overall conclusions are similar to the EAG preferred base case. |
| Page 45: "*However, at clarification, the EAG did notice that the PFS and TOT curves for trifluridine-tipiracil monotherapy crossed for a small proportion of patients due to the uncertainty in extrapolation. Despite the minimal impact on the ICER, the company* | "*However, at clarification, the EAG did notice that the PFS and TOT curves for trifluridine-tipiracil monotherapy crossed for a small proportion of patients due to the uncertainty in extrapolation.* | The original model included the ToT cap at PFS and was therefore not | Text amended as suggested. |

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| *subsequently capped TOT at PFS to ensure that treatment does not continue beyond progression, and this is incorporated within the company's revised base case post clarification. Despite only having a minor impact on the ICER, the EAG considers the company's capping of ToT at PFS to be appropriate."*<br><br>Page 66: *"The company made some minor changes to their preferred base case in response to clarification queries, applying an updated NMA and applying a cap of the ToT curves to ensure they fall below PFS."*<br><br>These statements are incorrect. The company did not update this at clarification stage as the ToT was already capped in the model for the original submission. See company response to clarification question B.3:<br><br>*"Although the extrapolations of PFS and ToT may cross, to ensure this does not occur in the model (as a result of modelling PFS and ToT separately), ToT is capped by PFS (applied within the "P-Flow" sheets), so that ToT can never exceed PFS (in line with the license and expected use within practice). This capped approach means that there is no occurrence of PFS and ToT crossing which feed into the modelled outcomes. The resulting curves after capping which inform* | *However the company confirmed that the model caps TOT at PFS to ensure that treatment does not continue beyond progression. The EAG considers the company's capping of ToT at PFS to be appropriate"*<br><br>*"The company made some minor changes to their preferred base case in response to clarification queries, applying an updated NMA."* | subsequently changed at clarification stage. | |

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| *model results can be found on the "Validation" sheet."* | | | |

**Issue 3 Text corrections**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
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| Page 1: "The relevant intervention is Lonsurf plus avastin"<br>Missing biosimilars | *"The relevant intervention is Lonsurf plus avastin (or a biosimiar)* | Biosimilars are now available and may be available at a cheaper cost thsn avastin | Text amended as suggested. |
| Page 16: "In general, the baseline demographic characteristics were similar between the groups. There were more males (54.5%) than females (45.5%) in the trifluridine-tipiracil monotherapy group but there were similar proportions in the intervention group (49.6% and 45.5%, respectively)."<br>Incorrect figure | "In general, the baseline demographic characteristics were similar between the groups. There were more males (54.5%) than females (45.5%) in the trifluridine-tipiracil monotherapy group but there were similar proportions in the intervention group (49.6% and 50.4%, respectively)." | To use correct figure | Text amended as suggested |
| Page 30: *"For regorafenib, OS and PFS were obtained from a random-effects NMA, and time on treatment (ToT) was assumed equal to PFS."*<br>Missing best supportive care from descriptions | *"For regorafenib and BSC, OS and PFS were obtained from a random-effects NMA, and for regorafenib time on treatment (ToT) was assumed equal to PFS."* | To clarify what was used for BSC as well as regorafenib | Text amended as suggested |

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| Page 37: *"The HRs applied were 0.61 (0.36, 1.06) and 0.42 (0.27,0.64) for trifluridine-tipiracil + bevacizumab compared to regorafenib and BSC, respectively"*<br>The HRs reported are based on the original submission. These were subsequently updated at clarification stage. | *"The HRs applied were 0.60 (0.38, 0.95) and 0.41 (0.28,0.58) for trifluridine-tipiracil + bevacizumab compared to regorafenib and BSC respectively".* | To correct the HRs used in the company's base case | Text amended as suggested |
| Page 45: *"From the preferred base case random-effects NMA for PFS (updated post clarification queries), hazard ratios of 0.47 (0.29,0.82) and 0.2 (0.13,0.31) were applied to regorafenib and BSC respectively."*<br>The HRs reported are based on the original submission. These were subsequently updated at clarification stage. | *"From the preferred base case random-effects NMA for PFS (updated post clarification queries), hazard ratios of 0.49 (0.31,0.84) and 0.21 (0.14,0.31) were applied to regorafenib and BSC respectively."* | To correct the HRs used in the company's base case | Text amended as suggested. |
| Page 46: "*Data are assessed against the CORRECT, rather than the CONCUR study for regorafenib because the former are used to estimate the PFS curves, and it is important to ensure consistency between data sources for comparison."*<br>It is not clear in this sentence that CORRECT is only used in the EAG base case PFS curves. | "*Data are assessed against the CORRECT, rather than the CONCUR study for regorafenib because the former are used to estimate the PFS curves in the EAG base case, and it is important to ensure consistency between data sources for comparison."* | To clarify that CORRECT is only used in the EAG's base case PFS curves | Not a factual inaccuracy.<br>However, text amended as suggested to improve clarity. |
| Page 53: "*The EAG agrees with the company that the same approach should be taken for both the pre-progression and post-* | "*The EAG agrees with the company regarding the concerns in counterintuitive results. As such the* | The statement could be misleading. | Not a factual inaccuracy. |

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| *progression health state utility values and that the same decline post progression should be modelled for both treatment arms."*<br><br>This statement is misleading as it implies the company stated that the same approach should be used for pre- and post-progression utilities. In response to clarification question B5, the company pointed out the rationale for higher PF utilities based on strong clinical opinion that pre-progression utility would be higher for the trifluridine-tipiracil plus bevacizumab arm. The company then highlighted concern that using the same PP utilities results in implausible decline for the intervention arm compared to the comparator. | *EAG believe that the same approach should be taken for both the pre-progression and post-progression health state utility values and that the same decline post progression should be modelled for both treatment arms."* | | However, text amended as suggested to improve clarity. |
| Page 54: *"Adverse events for regorafenib were sourced from TA866, based on the CORRECT study"*<br><br>Incorrect statement | *"Adverse events for regorafenib and BSC were sourced from TA866, based on the pooled CORRECT and CONCUR study"* | To correct the source used for adverse events and to clarify what was used for BSC as well as regorafenib | Text amended as suggested |
| Page 65 Table 65.<br><br>The EAG's post-progression treatment cost reported in the table for regorafenib is incorrect | Amend £4,745.54 to £2,110.78 | Correction | Thank you for noting this typo in the final row, last column of Table 25. The table has been updated to include the correct figure. The EAG can confirm that the correct figures are included in the economic |

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| | | | model and all tables of results. |
| Page 65: *"The intervention technology (trifluridine-tipiracil + bevacizumab) generates higher QALY gains than trifluridine-tipiracil monotherapy or regorafenib across a wide range of scenario analyses."*<br>*"The intervention technology is also more costly than trifluridine-tipiracil monotherapy or regorafenib…"*<br>BSC is missed from these statements | *"The intervention technology (trifluridine-tipiracil + bevacizumab) generates higher QALY gains than trifluridine-tipiracil monotherapy, BSC or regorafenib across a wide range of scenario analyses."*<br>*"The intervention technology is also more costly than trifluridine-tipiracil monotherapy, BSC or regorafenib…"* | To clarify results against BSC as well as regorafenib and trifluridine-tipiracil monotherapy | Not a factual inaccuracy.<br>However, the quoted text on page 66 is updated as suggested for completeness. |
| Page 68 Table 26 and Table 27. The results of Subgroup results – no prior bevacizumab presented in the EAG report are incorrect. The base case should be reset if the population is changed from 'ITT' to 'No prior bevacizumab' in the economic model. Details of the no prior bevacizumab base case is presented in the company submission Appendix M. | The correct results for the no prior bevacizumab subgroup are presented at the end of this document. | Incorrect results | Thank you for flagging the need to reset the company original base case settings before implementing the subgroup analysis. Corrected figures are now provided in Tables 26 and 27. An additional footnote has been added to these tables to explain the need to reset the model base case settings prior to implementing this scenario. |
| Page 98 Table 33<br>There is an inconsistency in the company and EAG results used to check the severity | This does not amend the conclusion of the severity modifier, however the EAG should be consistent in the use | Inconsistency in reporting | Table 33 updated to apply calculations based on deterministic results in both |

| | | | |
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| modifier. The EAG results are probabilistic and company's results are deterministic. | of deterministic or probabilistic values used. Please amend the EAG's QALYs to deterministic or the company's QALYs to probabilistic. | | cases. The EAG can confirm that the findings of the probabilistic analyses are similar. |

**Issue 4 Clarification points**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 51: "*At clarification stage, the EAG asked the company to provide the results of a repeated measures model, but it is unclear whether the results provided in the company's clarification response are from the original mixed effects model or a revised repeated measures modelling approach. Further clarification on this point would be appreciated."* | The results of the utility analyses provided at clarification stage used the same model as per the original submission i.e., mixed effects model. This model was produced in R using the "lmer" function. The "lmer" function in R is used for fitting linear mixed-effects models, so it falls under the category of mixed effects models. It allows you to specify both fixed effects (e.g., treatment effects) and random effects (e.g., subject-specific intercepts or slopes) in the model formula, making it a versatile tool for analyzing data with repeated measurements or hierarchical structures. As such, the company felt that repeated measures were | EAG request for clarification | The EAG appreciates the additional clarification provided and is satisfied that the mixed-effects model implemented in R is appropriate for estimating utilities. This is now noted in the EAG report (page 52). |

| | | | |
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| | incorporated into the utility models provided. | | |
| Page 60: "*The EAG notes that the costing year and underlying source of unit costs are different to those considered in the rest of the submission."*<br><br>*"Furthermore, the subsequent costs are higher than the initial costs, likely because the subsequent chemotherapy delivery HRG code SB15Z covers a range of complexity of subsequent treatments, whereas the initial administration code (SB12Z) covers simple parenteral chemotherapy. The EAG would expect the costs of subsequent deliveries to be lower, as they likely require a shorter appointment."* | The company would like to clarify that the source used for the admin scenario in response to clarification question B8 was used in line with the source used in the NHS England budget impact analyses (received after company submission) and that all the administration costs were changed to use this source in the scenario (which includes the subsequent treatment cost administrations).<br><br>The company agree with the EAG that the HRG code SB15Z would be expected to be lower than the initial administration SB12Z due to a shorter appointment. Using the National Cost Collection 21-22 data, using the 'Other' administration costs results in a slightly lower SB15Z cost versus SB12Z which may be considered more plausible. This issue was also raised by the EAG in TA946, where the EAG considered the | Further clarity on administration costs | The EAG appreciates the additional clarification from the company and additional scenario analyses around this issue.<br><br>Upon further inspection of the additional analyses provided, the EAG agrees that the company's alternative suggestion to use HRG SB12Z (other), £188.06 for day 1 and SB15Z (other), £186.56 for day 15 of each 28-day cycle could be a plausible, lower cost, alternative.<br><br>The EAG has added an additional analysis to Tables 31 and 32, applying a plausible, alternative lower cost of treatment administration to the EAG preferred base case analysis, for |

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| | company's administration costs could be overestimated due to the cost increase between the 2018-19 NHS costs to the 2019-20 NHS costs for initial and subsequent chemotherapy administration. The EAG, in TA946, concluded this may be due to the COVID-19 pandemic and believed the NHS costs from 19-20 uplifted should have been used to avoid bias from the pandemic. In light of the confusion and uncertainty associated with the most appropriate cost (and source) for consideration, alongside no technical engagement step in the NICE STA process for this appraisal, the company have presented some scenarios using alternative administration cost sources (Table 3). | | the committee's information. |

| Location of incorrect marking | Description of incorrect marking | Amended marking | EAG response |
|---|---|---|---|
| **Page 66. No CIC marking needed** | *"The calculated QALY weightings for comparisons against trifluridine-tipiracil is 1.2 (based on a proportional shortfall of [redacted]) and 1.7 for comparisons against regorafenib and BSC (proportional shortfall >95%)."* | *"The calculated QALY weightings for comparisons against trifluridine-tipiracil is 1.2 (based on a proportional shortfall of 94.84%) and 1.7 for comparisons against regorafenib and BSC (proportional shortfall >95%)."* | *Confidential marking removed as suggested. The EAG has also removed all confidential marking from Table 33.* |

**Table 1: Table 26 Base case and scenario analyses (pairwise comparisons) conducted by the company [reproduced from Tables 5, 8, 9 10 and 18 of the company's clarification response]**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Subgroup results -no prior bevacizumab** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.95 | 1.33 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 1.00 | 0.71 | 0.85 | 1.20 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.89 | 0.59 | [redacted] | 1.07 | 0.74 | 0.89 | 1.26 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 1.20 | 0.80 | [redacted] | 0.75 | 0.53 | 0.64 | 0.91 | [redacted] | [redacted] | [redacted] |

**Table 2: Table 27 Base case and scenario analyses (fully incremental) conducted by the company [reproduced from Tables 6, 7, 19 and the model from the company's clarification response]**

| Technologies | Total | | Incremental | | ICER incremental (£/QALY) x1.0 | ICER incremental (£/QALY) x1.2 | ICER incremental (£/QALY) x1.7 |
|---|---|---|---|---|---|---|---|
| | Costs (£) | QALYs | Costs (£) | QALYs | | | |
| **Subgroup results– no prior bevacizumab** | | | | | | | |
| BSC | [redacted] | 0.591 | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.624 | [redacted] | 0.033 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.797 | [redacted] | 0.206 | [redacted] | [redacted] | [redacted] |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.330 | [redacted] | 0.739 | [redacted] | [redacted] | [redacted] |

**Table 3: Scenarios using alternative administration sources (pairwise comparisons)**

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| **Company base case (SB12Z £286.71 day 1 and 15 of 28-day cycle– NHS cost collection 21-22 – Total HRGs)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Scenario (SB12Z £167 day 1 and SB15Z £334 day 15 of 28-day cycle – NHS Payment scheme 23/25)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |

| Technologies | Total | | | Incremental | | | | | ICER (£/QALY) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Costs (£) | LYG | QALYs | Costs (£) | LYG | QALYs | | | | | |
| | | | | | | x1.0 | x1.2 | x1.7 | x1.0 | x1.2 | x1.7 |
| BSC | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Scenario (SB12Z £188.06 day 1 and SB15Z £186.56 day 15 of 28-day cycle – NHS cost collection 21-22 – Other)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Scenario (SB12Z £227.87 day 1 and SB15Z £261.25 day 15 of 28-day cycle – NHS cost collection 19-20 uplifted to 21/22 costs – Outpatient)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |
| **Scenario (SB12Z £169.99 day 1 and SB15Z £175.96 day 15 of 28-day cycle – NHS cost collection 19-20 uplifted to 21/22 costs – Other)** | | | | | | | | | | | |
| Trifluridine-tipiracil + bevacizumab | [redacted] | 1.35 | 0.94 | | | | | | | | |
| Trifluridine-tipiracil | [redacted] | 0.95 | 0.62 | [redacted] | 0.41 | 0.32 | 0.39 | 0.55 | [redacted] | [redacted] | [redacted] |
| Regorafenib | [redacted] | 0.63 | 0.42 | [redacted] | 0.73 | 0.52 | 0.62 | 0.88 | [redacted] | [redacted] | [redacted] |
| BSC | [redacted] | 0.83 | 0.56 | [redacted] | 0.52 | 0.38 | 0.46 | 0.65 | [redacted] | [redacted] | [redacted] |

**Single Technology Appraisal**

**Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **5 March 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

**Issue 1 Clarification of EAG base case for trifluridine-tipiracil**

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| Page 3:<br>"*For these reasons, the EAG prefers the Weibull as the most appropriate curve to estimate OS for both trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil."*<br>*Table 1 & Table 2* | "*For these reasons, the EAG prefers the Weibull as the most appropriate curve to estimate OS for trifluridine-tipiracil + bevacizumab. For trifluridine-tipiracil, the EAG prefer to use the HR derived from the NMA"*<br>*Table 1 and Table 2 should be corrected to show the % survival and progression-free using the NMA HR for trifluridine-tipiracil.* | The EAG base case does not use Weibull for trifluridine-tipiracil monotherapy. | After further assessment of the results, the EAG considered it more appropriate to apply the HRs for the subgroup analysis of no prior bevacizumab because comparable subgroup data were not available from the comparator trials for regorafenib. Unfortunately the text, Table 1 and Table 2 were not updated to explain this. We thank the company for noticing the discrepancy and have updated the text, Table 1 and Table 2 accordingly. |
| Page 6, Table 3:<br>The EAG's base case for trifluridine-tipiracil is not correctly reported. | Trifluridine-tipiracil OS and PFS is informed by Log-normal curve in the company's base case and HRs from NMA in the EAG's base case. | Correction to table required. | Thank you for the comment. We have made the suggested amendment. |

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