Trifluridine/tipiracil (Lonsurf®, TAS-02) with bevacizumab for the treatment of metastatic colorectal cancer (CRC)

General information

Drug description [1]

Lonsurf® is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride. Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, tipiracil hydrochloride.

Indication [2]

Trifluridine / tipiracil (Lonsurf®, TAS-02) is indicated in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

Incidence

In Austria, in 2020 the age-standardised incidence rate[1] of cancer of the colon and rectum was 61.5/100,000 men and 38.0/100,000 in women. In 2020, a total of 4,427 persons were newly diagnosed with cancer of the colon and rectum [2].
The mean age at diagnosis of colon cancer is 70-75 years [3].
Approximately 20% of patients with CRC have metastases at the time of diagnosis, whereas up to 50% of patients with initially localised disease will develop metastases [4].

Current treatment [3]

- **For the second-, third- and fourth-line therapy of stage IV colon cancer, Onkopedia recommends:**
  - For patients whose tumour disease progresses after first-line therapy, further treatment is determined by prior therapy, therapy goal, BRAF and RAS status, and MSI status.
  - Second-, third-, or fourth-line therapy is individualised.
  - The following principles should be considered:
    - After therapy with first-line irinotecan-based therapy, oxaliplatin should be used in combination with a fluoropyrimidine.
    - After prior therapy with oxaliplatin, irinotecan should be combined with a fluoropyrimidine.
    - If a bevacizumab-free irinotecan-based therapy was chosen in the first-line setting, FOLFOX+ bevacizumab should be used in the second-line setting.
    - Continuation of bevacizumab beyond progression on first-line therapy significantly prolongs OS.
    - For patients previously treated with oxaliplatin-based therapy, FOLFIRI chemotherapy can be combined with the anti-angiogenic agent aflibercept. This results in a statistically significant prolongation of survival.
    - In second-line therapy, the combination of the antiangiogenic antibody ramucirumab with FOLFIRI leads to prolonged survival in patients treated with first line oxaliplatin- and bevacizumab-based therapy.
    - Ramucirumab or aflibercept should be preferred in patients with only a short first-line PFS on bevacizumab-containing therapy.
    - Patients with RAS wild-type, who have not received anti-EGFR antibody in first-line therapy and have a high remission pressure for second-line therapy, should be treated with a combination of an anti-EGFR antibody plus chemotherapy, see Colon cancer treatment protocols. This includes switching cytostatic agents.
    - Cetuximab and panitumumab should preferably be used in first-line therapy. When used for the first time in chemotherapy-refractory patients, both agents are equieffective. The use of panitumumab after failure of cetuximab-based regimens is no standard of care, and this also applies vice versa. Re-challenge of cetuximab or panitumumab should only be performed in patients with no detectable RAS and/or BRAF mutations on liquid biopsy.
    - In patients with BRAF V600E mutation, the use of a combination of encorafenib and cetuximab in second- and third-line therapy in accordance with current approval results in a prolongation of PFS and OS.
    - After pretreatment with chemotherapy, the combination of nivolumab and ipilimumab can be used in patients with MSI-high tumours in accordance with current approval.

[1] European Standard Population 2013.

- When all established chemotherapies and monoclonal antibodies fail, the oral multikinase inhibitor regorafenib or trifluridine/tipiracil prolong overall survival.
- For patients with HER2 positivity (especially after anti-EGFR therapy and in left-sided tumours), there is a treatment option with trastuzumab/lapatinib, trastuzumab/pertuzumab or trastuzumab-deruxtecan. However, approvals of these drugs for this treatment setting are pending.
- Patients whose tumour has an NTRK fusion can be treated with the tyrosine kinase inhibitors larotrectinib or entrectinib in accordance with their approval.
- For all phases of drug-based tumour therapy, the occurrence of adverse effects should be monitored regularly, i.e., at each therapy cycle, by history, clinical examination, and laboratory analyses. The response to the systemic tumour therapy is monitored every 2 to 3 months by clinical examination and targeted, imaging diagnostics.

Regulatory status

EMA [5]	FDA [6, 7]
Approval status for this indication: On 22 June 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Lonsurf®. The CHMP adopted a new indication as follows: ❖ Lonsurf® is indicated in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. **Other indications**: ❖ Lonsurf® is indicated as monotherapy for the treatment of adult patients with metastatic CRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. ❖ Lonsurf® is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.	**Approval status for this indication**: In April 2023, the FDA has granted priority review to a supplemental new drug application for trifluridine plus tipiracil (Lonsurf®) in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, an anti-EGFR therapy, or if they are RAS wild-type. UPDATE 10/2023: Lonsurf is indicated for the treatment of adult patients with metastatic CRC as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy . **Other indications**: Lonsurf® is indicated for the treatment of adult patients with: ❖ metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

Manufacturer

Lonsurf® is manufactured by Les Laboratoires Servier.

Costs [8]

20 Lonsurf® tablets 15mg[2]/6.14mg[3] = € 564.76 (ex-factory price)
20 Lonsurf® tablets 20mg/8.19mg = € 736.69 (ex-factory price)

Warnings and precautions

❖ **Bone marrow suppression**
- Lonsurf® caused an increase in the incidence of myelosuppression including anaemia, neutropenia, leukopenia, and thrombocytopenia.
- Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor toxicity, but at a minimum, prior to each treatment cycle.
- Treatment must not be started if the absolute neutrophil count is < 1.5 x 10^9/L, if the platelet counts are< 75 x 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-haematological clinically relevant toxicity from prior therapies.
- Serious infections have been reported following treatment with Lonsurf®.

[2] Trifluridine
[3] Tipiracil (as hydrochloride)

- Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated.
- In RECOURSE and TAGS studies, 9.4% and 17.3% of patients in the Lonsurf® group respectively received G-CSF mainly for therapeutic use.

❖ **Gastrointestinal toxicity**
- Lonsurf® caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhoea.
- Patients with nausea, vomiting, diarrhoea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrhoeal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated.
- Dose modifications (delay and/or reduction) should be applied as necessary.

❖ **Renal impairment**
- Lonsurf® is not recommended for use in patients with end-stage renal disease (CrCl < 15 mL/min or requiring dialysis), as Lonsurf® has not been studied in these patients.
- The global incidence of AEs is similar in normal renal function (CrCl ≥ 90 mL/min), mild (CrCl = 60 to 89 mL/min) or moderate (CrCl = 30 to 59 mL/min) renal impairment subgroups.
- However, the incidence of serious, severe AEs and AEs leading to dose modification tends to increase with advancing levels of renal impairment. In addition, a higher exposure of trifluridine and tipiracil hydrochloride was observed in patients with moderate renal impairment, compared with patients with normal renal function or patients with mild renal impairment.
- Patients with severe renal impairment (CrCl = 15 to 29 mL/min) and adjusted starting dose of 20 mg/m^{2}twice daily had a safety profile consistent with the safety profile of Lonsurf® in patients with normal renal function or mild renal impairment. Their exposure to trifluridine was similar to that of patients with normal renal function and their exposure to tipiracil hydrochloride was increased compared to patients with normal renal function, mild and moderate renal impairment.
- Patients with renal impairment should be monitored closely when being treated with Lonsurf®; patients with moderate or severe renal impairment should be more frequently monitored for haematological toxicities.

❖ **Hepatic impairment**
- Lonsurf® is not recommended for use in patients with baseline moderate or severe hepatic impairment (NCI Criteria Group C and D defined by total bilirubin > 1.5 x ULN), as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment, although this is based on very limited data.

❖ **Proteinuria**
- Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy.

❖ **Lactose intolerance**
- Lonsurf® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

❖ **Embryo-fetal toxicity**
- Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Study characteristics [9-12]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
SUNLIGHT NCT04737187	492 (1:1)	trifluridine–tipiracil + bevacizumab	trifluridine–tipiracil alone	OS	14.2 months vs. 13.6 months	**ongoing[4],** randomised, open-label, phase 3 trial	-	Servier and Taiho Oncology	SUNLIGHT trial [12]

Inclusion criteria[5]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Patients aged ≥18 years with histologically confirmed unresectable adenocarcinoma of the colon or rectum.	❖ More than 2 prior chemotherapy regimens for the treatment of advanced CRC.	❖ Median age: 62 vs. 64 years ❖ Male sex: 49.6% vs. 54.5%

[4] The SUNLIGHT trial is ongoing until September 2023.
[5] For detailed in- and exclusion criteria, please see trial protocol.

❖ Previously determined RAS status. ❖ Patient received a maximum of 2 prior chemotherapy regimens for the treatment of advanced CRC and had demonstrated progressive disease or intolerance to their last regimen. ❖ Measurable or non-measurable disease as defined by RECIST version 1.1. ❖ Ability to swallow oral tablets. ❖ Estimated life expectancy ≥12 weeks ❖ ECOG PS ≤1 ❖ Adequate organ function within 7 days prior to randomisation. ❖ Female of childbearing potential must have been tested negative in a serum pregnancy test within 7 days prior to randomisation. ❖ Female of childbearing potential and males with partners of childbearing potential must agree to use a highly effective method of birth control. ❖ Written informed consent obtained prior to any study-specific procedure.	❖ Pregnancy, lactating female, or possibility of becoming pregnant during the study. ❖ Patients currently receiving or having received anticancer therapies within 4 weeks prior to randomisation. ❖ Patients who have not recovered from clinically relevant non-hematologic CTCAE grade ≥ 3 toxicity of previous anticancer therapy prior to randomisation (excluding alopecia, and skin pigmentation). ❖ Symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease. ❖ Major surgery within 4 weeks prior to randomisation. ❖ Severe or uncontrolled active acute or chronic infection. ❖ Active or history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension. ❖ Hepatitis B Virus infection/ Hepatitis C Virus infection/ Carriers of HIV antibodies. ❖ Uncontrolled diabetes mellitus/arterial hypertension/ symptomatic arrhythmia. ❖ Deep arterial thromboembolic events within the last 6 months prior to randomisation. ❖ Severe/unstable angina, symptomatic CHF NYHA class III or IV. ❖ Treatment with systemic immunosuppressive therapy. ❖ Prior radiotherapy if completed less than 4 weeks before randomisation. ❖ Previously received trifluridine/tipiracil. ❖ Deep venous thromboembolic event within 4 weeks prior to randomisation. ❖ Known coagulopathy that increases risk of bleeding, bleeding diatheses.	❖ Race or ethnic group: • White: 87.4% vs. 89.4% • Black: 1.6% vs. 1.2% • Asian: 0% vs. 0.4% • American Indian or Alaska Native: 0.4% vs. 0% • Other: 3.3% vs. 2.0% • Unknown: 7.3% vs. 6.9% ❖ Primary diagnosis • Colon cancer: 73.2% vs. 73.6% • Rectal cancer: 26.8% vs. 26.4% ❖ Median duration of disease: • 2.0 years vs. 2.1 years ❖ Time from diagnosis of first metastasis to randomisation: • <18 months: 42.3% vs. 42.7% • ≥18 months: 57.7% vs. 57.3% ❖ Number of sites of metastasis: • 1 or 2: 61.8% vs. 57.3% • ≥3: 38.2 vs. 42.7% ❖ Previous treatments received for metastatic disease: • Fluoropyrimidine: 100.0% vs. 100.0% • Irinotecan: 100.0% vs. 99.6% • Oxaliplatin: 98.0% vs. 98.8% ❖ Anti-VEGF monoclonal antibody: 72.4% vs. 71.5% ❖ Anti-EGFR monoclonal antibody: 94.4% vs. 93.0% ❖ ECOG performance-status score: • 0: 48.4% vs. 43.1% • 1: 51.6% vs. 56.5% • 2: 0% vs. 0.4%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Median follow-up: 14.2 months (IQR, 12.6-16.4) vs. 13.6 months (IQR, 12.7-15.9):</u> **Median OS**: 10.8 months (95% CI, 9.4-11.8) vs. 7.5 months (95% CI, 6.3-8.6); HR for death 0.61; 95% CI, 0.49-0.77, p<0.001 **Median OS in sensitivity analysis** that excluded patients who did not meet relevant prespecified medical and therapeutic criteria: 10.8 months (95% CI, 9.6.-12.1) vs. 7.2 months (95% CI, 6.3-8.5); HR for death 0.59; 95% CI, 0.47-0.74 **6-month OS rates**: 77% vs. 61% **12-month OS rates**: 43% vs. 30% **Median PFS**: 5.6 months (95% CI, 4.5-5.9) vs. 2.4 months (95% CI, 2.1-3.2); HR for disease progression or death 0.44; 95% CI, 0.36-0.54; p<0.001 **6-month PFS rates**: 43% vs.16%	**AEs of any cause:** 98% vs. 98% **Severe AEs grade ≥3:** 72.4% vs. 69.5% **Serious AEs:** 24.8% vs. 31.3% **Administration of concomitant GCS-F:** 29.3% vs. 19.5% **AEs that were attributed by the investigator to trifluridine-tipiracil:** 89.8% vs. 81.3% **AEs that were bevacizumab-related:** 48.4% **Treatment-related deaths:** 0 vs. 0

12-month PFS rates: 16% vs. 1% **ORR**: 6.1% (95% CI, 3.5-9.9, 15 patients with PR) vs. 1.2% (95% CI, 0.3-3.5, 1 CR and 2 PR); between-group difference 4.9 percentage points; 95% CI, 1.6-8.2)	**AEs of any cause that leading to discontinuation of the trial regimen:** 12.6% vs. 12.6%[6] **Median time to worsening of the ECOG PS score from 0 or 1 to 2 or more:** 9.3 months (95% CI, 8.3-10.6) vs. 6.3 months (95% CI, 5.6-7.2); HR 0.54, 95% CI, 0.43-0.67

Patient-reported outcomes (Poster data) [13]

- According to the SUNLIGHT study protocol, QoL is assessed by two questionnaires (EORTC QLQ-C30 and EQ-5D-5L).
- HRQoL was evaluated at baseline, at each cycle, and at withdrawal visit using EORTC QLQ-C30 and EuroQol EQ-5D-5L questionnaires
- QoL outcomes analysis 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.
- Among 492 randomised patients, 239 and 241 (i.e., a total of >97.6%) had QoL data at baseline in I and C, respectively.
- HRQoL data are presented for the first 6 cycles, as questionnaire completion rates dropped to less than 10% after this time-point, which did not allow for a meaningful interpretation of the results.
- Cancer-related (QLQ-C30) and general (EQ-5D-5L) HRQoL were maintained from baseline to cycle 6, and no clinically relevant changes in mean scores were observed in any sub-domains.
- QLQ-C30 GHS scores also showed no deterioration in either arm.
- Patients receiving trifluridine/tipiracil plus bevacizumab had a reduced risk of GHS definitive worsening of more than 10 points (median time to worsening in GHS was 8.5 months in I vs. 4.7 months in C (HR 0.50; 95% CI, 0.38-0.65) and in all scales and subscales.
- In a sensitivity analysis considering disease progression as a definitive deterioration measured by QLQ-C30, HRQoL deteriorated significantly later: median time to deterioration in I was 4.5 months vs. 2.07 months in C (HR 0.49; 95% CI, 0.40-0.60), consistently favouring I.
- A similar result was observed with the EQ-5D-5L utility score and VAS, showing that HRQoL deteriorated later in patients treated with trifluridine/tipiracilplus bevacizumab compared to those treated with trifluridine/tipiracil monotherapy.
- The OS/PFS benefits of trifluridine/tipiracil plus bevacizumab as third-line treatment of mCRC are associated with maintenance of QoL.
- EQ-5D-5L and QLQ-C30 HRQoL were maintained from baseline to cycle 6 with no clinically relevant changes in mean scores observed in any sub-domains.
- There was a trend towards a more prolonged time to definitive deterioration of HRQoL scales and subscales in I vs. C.

ESMO-MCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +3.3 months	0.61 (0.49-0.77)	HR≤0.65 AND gain ≥3.3 months	4	-	-	-	4
Adapted	NC	2a	≤12 months	OS: +3.3 months	0.61 (0.49-0.77)	HR≤0.65 AND gain ≥3.3 months	4	-	-	-	4

Risk of bias (RCT) [15]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	no[7] high risk	unclear[8] unclear risk	yes[9] high risk	**unclear**

Ongoing trials [16]

NCT number/trial name	Description	Estimated study completion date

6 Of these events, the investigators determined that the events were related to treatment in 2.4% and 2.0%, respectively.

[7] SUNLIGHT is an open-label trial.

[8] The SUNLIGHT trial is currently ongoing; hence, final analysis data is not yet available.

[9] The trial was sponsored by Servier and Taiho Oncology and designed by the last author and representatives of Servier. The sponsors were involved in the design and conduct of the trial, the collection and analysis of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. The first draft of the manuscript was written by a medical writer, funded by the sponsors. Data confidentiality agreements were in place between the authors and the sponsors.

NCT04737187/ SUNLIGHT	Please see above.	09/2023
NCT04457297/ ALTAIR	A randomised, double-Blind, phase III study comparing trifluridine/tipiracil therapy vs. placebo in patients who are positive for blood circulating tumour DNA after curative resection of CRC.	12/2023
NCT05223673/ COLSTAR	A randomised, open-label, multi-centre, two-arm phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a safety lead-in part in participants with KRAS/NRAS and BRAF wild type metastatic CRC previously treated with standard treatment and anti-EGFR therapy.	10/2026

Available assessments

No assessments, evaluating the combination therapy of trifluridine/tipiracil with bevacizumab were identified.

Other aspects and conclusions

- In June 2023, the **CHMP adopted a new indication** for Lonsurf®, indicated in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. Lonsurf® is currently not approved for this indication in the U.S.; in April 2023, the **FDA has granted priority review** to a supplemental new drug application for trifluridine plus tipiracil (Lonsurf®) in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, an anti-EGFR therapy, or if they are RAS wild-type. UPDATE: The FDA approved Lonsurf® for this indication in August 2023.
- The **ongoing**, open-label, randomised phase III **SUNLIGHT trial** was designed to assess the efficacy and safety of trifluridine/tipiracil in combination with bevacizumab as compared with trifluridine/tipiracil alone in patients with refractory metastatic CRC. Patients with histologically confirmed, unresectable adenocarcinoma of the colon or rectum were included if they had received ≤2 previous chemotherapy regimens for the treatment of advanced CRC and had had progressive disease or if their last regimen had caused unacceptable adverse effects. For the wide range of in- and exclusion criteria, please see study protocol.
- OS was the **primary endpoint** of the SUNLIGHT trial: **Median OS** was 10.8 months in the patients who received trifluridine/tipiracil + bevacizumab as compared with 7.5 months in patients who received trifluridine/tipiracil alone (**HR for death 0.61; 95% CI, 0.49-0.77, p<0.001**).
- **QoL** analysis data is only available as a poster presentation.
- The original and adapted **ESMO-MCBS** were applied, each resulting in a final magnitude of clinical benefit of 4, indicating a substantial magnitude of clinical benefit of the combination of trifluridine/tipiracil and bevacizumab.
- Since the SUNLIGHT trial is currently ongoing and no final analysis data is available, the **risk of bias was considered unclear**. However, the risk of bias is increased by the open-label design and the involvement of the sponsor in trial design and data analysis.
- Beside the SUNLIGHT trial, 2 further ongoing phase III trials, evaluating trifluridine/tipiracil in patients with colorectal cancer were identified. 5 trials using trifluridine/tipiracil as comparator are currently ongoing (NCT04776148, NCT05064059, NCT05198934, NCT05600309 and NCT05328908).
- Final analysis data from SUNLIGHT, including QoL data, additional phase III data from other ongoing trials as well as long-term data are required for trifluridine/tipiracil (particularly in combination with bevacizumab) in patients with colorectal cancer.

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Abbreviations: AE=adverse event, AJ=adjustment, BRAF=v-Raf murine sarcoma viral oncogene homolog B, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHF=congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CRC=colorectal cancer, CrCl=creatinine clearance, CTCAE=Common terminology criteria for adverse events, DNA=deoxyribonucleic acid, ECOG PS=Eastern Cooperative Oncology Group performance status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L= EuroQol Group 5-Dimension 5-Level questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FOLFIRI=leucovorin calcium (folinic acid)+fluorouracil+irinotecan hydrochloride, FOLFOX=leucovorin calcium (folinic acid)+fluorouracil+oxaliplatin, G-BA=Gemeinsamer Bundesausschuss, G-CSF=Granulocyte colony-stimulating factor, GHS=global health status, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, MSI=microsatellite instability, n=number of patients, NA=not available, NCI=National Cancer Institute, NICE=National Institute for Health Care Excellence, NTRK=Neurotrophic tyrosine receptor kinase, NYHA=New York Heart Association, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RAS=Rat sarcoma viral oncogene homolog, RECIST=Response evaluation criteria in solid tumours, SAE=serious adverse event, ST=standard treatment, TPase=thymidine phosphorylase, ULN=Upper Limit of reference range, VEGF=vascular endothelial growth factor

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