Trifluridine/Tipiracil (Lonsurf)

Indication

Treatment of metastatic colorectal cancer in patients who have previously received or are not suitable for other available therapies including: fluoropyrimidine, oxaliplatin and irinotecan based chemotherapies.

Treatment of metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, in patients who have been previously treated with at least two prior systemic treatment regimens for advanced disease

ICD-10 codes

Codes prefixed with C16, C18-20.

Regimen details

Day	Drug	Dose	Route
1-5 and 8-12	Trifluridine/Tipiracil	35mg/m^2 BD *	Oral

***Doses are based on the trifluridine dose and are rounded to the nearest 5mg.**
Maximum dose is 80mg BD

Cycle frequency

28 days

Number of cycles

Continued until progression or unacceptable toxicity

Administration

Trifluridine/tipiracil is available as 15mg and 20mg tablets
15 mg tablet containing 15 mg /6.14 mg of trifluridine and tipiracil (as hydrochloride)
20mg tablet containing 20 mg /8.19 mg of trifluridine and tipiracil (as hydrochloride)

Tablets should be swallowed whole with a glass of water.

Pre-medication

Nil

Emetogenicity

This regimen has a moderate to low emetogenic potential

Additional supportive medication

Loperamide if required.
Anti-emetics if required
Topical emollients to prevent PPE
H2 antagonist or proton pump inhibitor if required

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Bone profile	14 days
CEA	14 days
Hepatitis B serology (HBsAG, HBcAb)	none
HbA1c	3 months
Random glucose	14 days

Investigations - pre subsequent cycles
FBC, U&E (including creatinine), LFT, random glucose, CEA

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 30 mL/min

Dose modifications
A maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m^2

Dose level	Dose
Full dose	35mg/ m^2 BD
First dose reduction	30mg/ m^2 BD
Second dose reduction	25mg/ m^2 BD
Third dose reduction	20mg/ m^2 BD

Once the dose has been reduced it should not be re-escalated.

No adjustment of the starting dose is required in patients ≥65 years old. Efficacy and safety data in patients over 75 years is limited.

- **Haematological toxicity**

Treatment should be withheld and recommenced as per the table below:

Haematological parameter	Interruption criteria	Resumption criteria
Neutrophils	<0.5 x 10^9/L	≥1.5 x 10^9/L
Platelets	<50 x 10^9/L	≥75 x 10^9/L

If febrile neutropenia or grade 4 neutropenia (< 0.5 x 10^9 /L) or thrombocytopenia (< 50 x 10^9 /L) resulting in more than 1 weeks delay to start of next treatment:
- withhold treatment until resolves to ≤ grade 1 or baseline
- resume dosing when neutrophils ≥ 1.5x10^9 /L and platelets ≥ 75x10^9 /L with 5mg/m^2 BD dose reduction (to a

minimum dose of 20mg/m^2 BD)

- **Renal impairment**

CrCl (mL/min)	**Dose**
≥ 30	35mg/m^2 BD
15-29	20mg/m^2 BD
<15	Contraindicated

For patients with severe renal impairment (15-29mL/min) starting dose of 20mg/m^2 BD is recommended. One dose reduction of 15mg/m^2 BD is permitted.

Dose escalation is not permitted after it has been reduced.

Administration is not recommended in patients with end stage renal disease (CrCl below 15mL/min or requiring dialysis) as there is no data available for these patients.

- **Hepatic impairment**

Trifluridine/Tipiracil is not recommended in patients with baseline moderate or severe hepatic impairment (bilirubin > 1.5 x ULN) as, a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment. No dose modification in mild hepatic impairment. Trifluridine/Tipiracil is not recommended in moderate-severe hepatic impairment (no data available for these patients).

- **Other toxicities**

Other ≥ grade 3 toxicities (except grade 3 nausea and/or vomiting controlled by anti-emetics or diarrhoea controlled by anti-diarrhoeals):
- withhold treatment until resolves to ≤ grade 1 or baseline
- resume with 5mg/m2 BD dose reduction (to a minimum dose of 20mg/m2 BD)

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Hepatotoxicity
Embolism

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Myelosuppression
Anorexia
Mucositis
PPE
Fatigue
Taste disturbance

- **Other side effects**

Dizziness
Stomatitis
Constipation
Headache
Alopecia
Rash

Deranged liver function
Peripheral neuropathy

Significant drug interactions – for full details consult product literature/ reference texts

Medicinal products that interact with nucleoside transporters CNT1, ENT1 and ENT2: use with caution, increased risk of toxicity.
Inhibitors of OCT2 or MATE1: use with caution, increased risk of toxicity.
Human thymidine kinase substrates, e.g., zidovudine: use with caution may reduce efficacy of trifluridine /tipiracil. If using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.
Hormonal contraceptives: it is unknown whether trifluridine /tipiracil may reduce the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptive must also use a barrier contraceptive method.

Additional comments

Trifluridine/Tipiracil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Trifluridine /Tipiracil.

Fertility/Contraception

Patients should use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breastfeeding should be discontinued during treatment. Women using hormonal contraceptive must also use a barrier contraceptive method.

References

- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 11 May 2022
- Summary of Product Characteristics Lonsurf®(Servier) accessed 18 May 2022 available at http://www.medicines.org.uk
- NICE TA405 (published 24 August 2016) accessed 18 May 2022 via www.nice.org.uk
- Mayer R Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. N Engl J Med 2015;372:1909-19.DOI: 10.1056/NEJMoa1414325

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER
RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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