PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Lonsurf (trifluridine and tipiracil)

Metastatic or locally advanced gastroesophageal and gastric adenocarcinoma

PROTOCOL REF: MPHALTTA
Version No. 1.0
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Approved for use in:

- Lonsurf (trifluridine–tipiracil) is recommended within its marketing authorisation, as an option for treating metastatic or locally advanced gastroesophageal and gastric adenocarcinoma that has failed at least two prior regimens for advanced/metastatic disease.
- Patients relapsing during neoadjuvant treatment and within 6 months of completing adjuvant chemotherapy can count the neoadjuvant /adjuvant line as one line of therapy for advanced/metastatic disease
- PS 0 – 1
- No swallowing difficulties

***** BLUETEQ REGISTRATION REQUIRED *****

Dosage

Drug	Dose	Route	Frequency	Duration
Lonsurf	**35mg/m^2**	Oral	Days 1 -5 **twice daily** Days 6-7 recovery Days 8-12 **twice daily** Days 13-28 recovery	**28 day cycle to continue until progressive disease, or toxicity or patient decision**

Administration

Day	Drug	Route	Dose
1 to 5	**Lonsurf**	**PO**	**35mg/m^2 twice daily after food**
6 to 7	Recovery	No treatment	
8 to 12	**Lonsurf**	**PO**	**35mg/m^2 twice daily after food**
13 to 28	Recovery	No treatment	

Tablets to be taken with a glass of water within one hour after completion of breakfast and evening meal.

Tablet dose is calculated based on the trifluridine dose and must be rounded to the nearest 5 mg dose band and supplied as a mixture of 15mg and 20mg tablets. The dosage must not exceed 80 mg/dose

Number of Lonsurf tablets per dose				
Lonsurf	BSA m^2	Dose in mg twice daily	Tablets per dose	
			15mg	20mg
35mg/m^2	<1.07	35	1	1
	1.07 – 1.22	40	0	2
	1.23 – 1.37	45	3	0
	1.38 – 1.52	50	2	1
	1.53 – 1.68	55	1	2
	1.69 – 1.83	60	0	3
	1.84 – 1.98	65	3	1
	1.99 – 2.14	70	2	2
	2.15 – 2.29	75	1	3
	≥2.30	80	0	4

Main toxicities	
Haematological	Neutropenia, thrombocytopenia, anaemia, leukopenia (spc-very common)
Gastrointestinal	Stomatitis, reflux, nausea, vomiting, constipation, diarrhoea, abdominal pain, Rare reactions <3% of patients - colitis, bowel obstruction haemorrhage
Cardiotoxicity	Rare reaction <3% of patients - Myocardial ischaemia, chest pain, bradycardia, tachycardia,
Hepatotoxicity	Elevated liver enzymes, hepatic failure, jaundice
Renal toxicity	Acute renal failure, hematuria
General disorders	Fatigue, myalgia, decreased appetite

Hepatic and renal impairment

Hepatic	Administration is not recommended in patients with baseline moderate or severe hepatic impairment i.e. if total bilirubin > 1.5 x ULN or Child Pugh B or C as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment.

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Child-Pugh Scoring

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

Child-Pugh Class
A (5-6 points)
B (7-9 points)
C (10 or more points)

Please note: al Normalised Ratio.

sessment of Child- is to help guide clinical scribing and pharmacists when screening.

Renal

Not recommended if <30ml/min

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Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X		Needs review pre C2	X	Will review pre C4 or C5 with CT scan results and if well tolerated Alternate Cycles or per clinical decision
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
CT scan	X				Baseline within 6 weeks of C1 day 1 and scan after C3 or C4 , if response scan every 3-4 months
Weight recorded	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Dose Reduction	Dosing
1st dose reduction	30 mg/m^2
2nd dose reduction	25 mg/m^2
3rd dose reduction	20 mg/m^2
See tables below	

Dose escalation is not permitted after it has been reduced.

For intolerable grade 2 or any toxicity or above grade 3, treatment should be withheld until toxicity resolves to grade 1 or 0. Treatment may then be restarted at a reduced dose level. Treatment may be held for up to 28 days. **If toxicities fail to resolve within 28 days treatment should be permanently discontinued**.

Hematological toxicity:

Unless different limits have been previously agreed by a consultant on an individual basis, proceed on day 1 if:-

Proceed on day 1 if-

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 75 x 10^9/L

For haematological toxicities treatment may be restarted at a reduced dose level when counts recover.

Adverse Reaction	**Recommended dose modifications**
Febrile neutropenia	Interrupt dosing until toxicity resolves to Grade 1 or baseline.
Grade 4 neutropenia (< 0.5 x 10^9 /L) or thrombocytopenia (< 25 × 10^9 /L) that results in more than 1 week's delay in start of next cycle	Resume dosing when neutrophils ≥ 1.5 × 10^9 /L and dose reduce by 5 mg/m^2 from the previous dose level
Platelets< 50 × 10^9 /L dose interrupt	Resuming dosing when Platelets≥ 75 × 10^9 /L and dose reduce

Non- Haematological toxicity

Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal medicines. Dose

reduce to next dosing level, do not increase dose. If toxicity not resolved dose reduce further.

Dose modifications

Level 1 dose reduction: Number of Lonsurf tablets per dose				
Lonsurf	BSA m^2	Dose in mg twice daily	Tablets per dose	
			15mg	20mg
30mg/m^2	<1.09	30	2	0
	1.09 – 1.24	35	1	1
	1.25 – 1.39	40	0	2
	1.40 – 1.54	45	3	0
	1.55 – 1.69	50	2	1
	1.70 – 1.94	55	1	2
	1.95 – 2.09	60	0	3
	2.10 – 2.28	65	3	1
	≥2. 29	70	2	2

Level 2 dose reduction: Number of Lonsurf tablets per dose				
Lonsurf	BSA m^2	Dose in mg twice daily	Tablets per dose	
			15mg	20mg
25mg/m^2	<1.10	25	2	1
	1.10 – 1.29	30	1 in the morning 1 in the evening	0
	1.30 – 1.49	35	1	1
	1.50 – 1.69	40	0	1 in the morning 1 in the evening
	1.70 – 1.89	45	1 in the morning 2 in the evening	0
	1.90 – 2.09	50	2	1
	2.10 – 2.29	55	1	2
	≥2. 30	60	1	3

Level 3 dose reduction number of Lonsurf tablets per dose			
Lonsurf	BSA m^2	Dose in mg twice daily	Tablets per dose

			15mg	20mg
20mg/m^2	<1.14	20	0	1
	1.14 – 1.34	25	2	1
	1.35 – 1.59	30	2	0
	1.60 – 1.94	35	1	1
	1.95 – 2.09	40	0	2
	2.10 – 2.34	45	3	0
	≥2. 35	50	2	1

References:

1. Electronic Medicines Compendium. Summary of product characteristics for trifluridine–tipiracil, https://www.medicines.org.uk/emc/product/7309 (accessed 20/1/23)
2. https://www.nice.org.uk/guidance/indevelopment/gid-ta11159
3. Lancet Oncol 2018 Nov;19(11):1437-1448. doi: 10.1016/S1470-2045(18)30739-3. Epub 2018 Oct 21. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
March 2023	V1.0	**Alia Alchawaf, Consultant & Gabriella Langton Advanced Pharmacist**	First version