BC Cancer Protocol Summary for Third- or Later-Line Therapy of Advanced Gastroesophageal Carcinoma Using Trifluridine-Tipiracil

Protocol Code	*UGIGAVTRFT*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY:
- Metastatic gastric cancer or adenocarcinoma of gastroesophageal junction
- ECOG 0-1
- At least two prior lines of therapy including fluoropyrimidine, platinum, taxane or irinotecan and HER2 directed therapy if positive – if relapse within 6 months of peri-operative or pre-operative treatment that will count as a line of therapy.
- A BC Cancer Compassionate Access Program (CAP) request with appropriate clinical information for each patient must be approved prior to treatment.

EXCLUSIONS:
- Patients with CNS metastases

TESTS:
- Baseline: CBC, differential, platelets, sodium, potassium, creatinine, urea, bilirubin, ALT, alkaline phosphatase, LDH, dipstick urine protein. Optional : CEA, 19-9
- Prior to each cycle: CBC, differential, platelets, sodium, potassium, creatinine, urea, bilirubin, ALT, alkaline phosphatase, LDH.
- Day 15 : CBC, differential and platelets
- If clinically indicated: dipstick urine protein, CEA, 19-9

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
trifluridine-tipiracil	35* mg/m^2 BID on days 1-5 and days 8-12	PO

* based on the trifluridine component; up to maximum of 80 mg/dose.

Repeat every 28 days (one cycle) until progression or unacceptable toxicity.

Dose Levels:

Starting dose	Dose level -1	Dose level -2	Dose level -3
35 mg/m^2	**30 mg/m^2**	**25 mg/m^2**	**20 mg/m^2**

- Dose escalation is not permitted after it has been dose reduced.
- Round dose to nearest 5 mg.
- A total daily dose of 50 mg should be taken as 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.

Suggested Dose Dispensing Table:

Dose (mg)* (given BID)	Number of Tablets per Dose	
	15 mg Tablet	20 mg Tablet
35	**1**	**1**
40	**0**	**2**
45	**3**	**0**
50	**2**	**1**
55	**1**	**2**
60	**0**	**3**
65	**3**	**1**
70	**2**	**2**
75	**1**	**3**
80	**0**	**4**

* based on the trifluridine component; up to maximum of 80 mg/dose.
15 mg tablet = trifluridine-tipiracil 15 mg-6.14 mg tablet
20 mg tablet = trifluridine-tipiracil 20 mg-8.19 mg tablet

DOSE MODIFICATIONS:

1. **Hematological:**
Table 1: Dose interruption and resumption criteria for hematological toxicities

Parameter	Interruption Criteria	Resumption Criteria*
ANC	Less than 0.5 x 10^9/L	Greater than or equal to 1.5 x 10^9/L
Platelets	Less than 50 x 10^9/L	Greater than or equal to 75 x 10^9/L

* Resumption Criteria applied to the start of the next cycle

Toxicity				Dose
Grade	**ANC ($x10^9$/L)**		**Platelets ($x10^9$/L)**	
1	greater than or equal to 1.5	or	greater than or equal to 75	100%
2	1.0 to less than 1.5	or	50 to less than 75	100%
3	0.5 to less than 1.0	or	25 to less than 50	100%
4	less than 0.5	or	less than 25	Delay until resolution to Grade 1 or baseline and then reduce one dose level. (minimum dose of 15 mg/m^2 twice daily in severe renal impairment)
Febrile neutropenia				Delay until resolution to Grade 1 or baseline and then reduce one dose level. (minimum dose of 15 mg/m^2 twice daily in severe renal impairment)

Dose escalation is not permitted after it has been dose reduced.

2. **Non-Hematological toxicity:**

CTCAE*- Grade	Dose
Grade 3 or 4 toxicity (except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responsive to antidiarrheal therapy)	Hold dose until symptoms resolve to Grade 1 or baseline and then reduce one dose level. (minimum dose of 15 mg/m^2 twice daily in severe renal impairment)
Interstitial Lung Disease/Pneumonitis (treatment-related)	Hold dose and investigate. If confirmed, discontinue treatment permanently.

* CTCAE : Common terminology criteria for adverse events.
Dose escalation is not permitted after it has been dose reduced.

3. **Renal dysfunction:**

Creatinine Clearance (mL/min)	Dosage recommendation
Greater than or equal to 60	No adjustment required
30 to 59	No adjustment required; monitor for increased hematologic toxicity
15 to 29	Recommend dose reduction to 20** mg/m^2 (based on the trifluridine component); monitor for increased hematologic toxicity
Less than 15	no information found

** Reduce dose to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily. Dose escalation should not be considered after the dose has been reduced. Permanently discontinue in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.

$$\text{calculated creatinine clearance} = \frac{\text{N* x (140 - Age) x weight in kg}}{\text{serum creatinine in micromol/L}}$$

For males N=1.23;
For females N=1.04

4. **Hepatic dysfunction**:

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). No information found in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). Higher incidence of grade 3 or 4 hyperbilirubinemia was observed in patients with baseline moderate hepatic impairment.

PRECAUTIONS:

1. Patients who received **prior radiotherapy** may be at higher risk of hematological and myelosuppression related adverse reaction including febrile neutropenia.

2. **Myelosuppression** can be severe and life-threatening. Fatal events related to neutropenic infection, sepsis, or septic shock have occurred. Monitor closely for signs of infection and treat as indicated.

3. **Pregnancy/Lactation:** Trifluridine-tipiracil is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose. Women using a hormonal contraceptive must also use a barrier contraceptive, as it is unknown whether trifluridine-tipiracil may reduce the effectiveness of hormonal contraceptives. Breastfeeding is not recommended during treatment and for one day following the final dose.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Shitara, K, Doi, T, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncol 2018; 19: 1437–1448.
2. LONSURF® Product monograph, Taiho Pharma Canada Inc. Submission Control No. 235999, Date of revision: 29 Oct 2020.