Regimen Monograph

A - Regimen Name

TRIFTIPI Regimen

Trifluridine/tipiracil

Disease Site
Gastrointestinal
Gastric / Stomach

Intent
Palliative

Regimen Category
Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
In combination with best supportive care for the treatment of non-resectable metastatic gastric cancer or adenocarcinoma of the gastroesophageal junction, in patients with ECOG status 0 or 1, who have experienced disease progression and/or intolerances with at least 2 prior lines of chemotherapy (Refer to EAP for details of funding criteria)

Supplementary Public Funding
trifluridine / tipiracil
Exceptional Access Program (For the treatment of metastatic gastric cancer (mGC) or adenocarcinoma of the gastroesophageal junction (GEJ) in adult patients, according to clinical criteria) (EAP Website)

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B - Drug Regimen

trifluridine / tipiracil	35* mg /m²	PO	BID on Days 1 to 5 and 8 to 12

*Based on the trifluridine component; up to a maximum of 80 mg per dose.

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low – No routine prophylaxis; PRN recommended

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Do not start treatment with trifluridine / tipiracil until ANC ≥ 1.5 x 10^9/L, platelets ≥ 75 x 10^9/L and non-hematological toxicities ≤ grade 1.

Dosage with toxicity

Dose Level	Dose* (mg/m^2) BID
0	35

-1	30
-2	25
-3	20
-4	Discontinue

*Based on trifluridine component

Dose Calculation Based on Body Surface Area (BSA)

Dose	BSA (m^2)	Dose (mg)*	Number of tablets per dose		Total daily dose (mg)*
			15 mg**	20 mg**	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 – 1.22	40	0	2	80
	1.23 – 1.37	45	3	0	90
	1.38 – 1.52	50	2	1	100
	1.53 – 1.68	55	1	2	110
	1.69 – 1.83	60	0	3	120
	1.84 – 1.98	65	3	1	130
	1.99 – 2.14	70	2	2	140
	2.15 – 2.29	75	1	3	150
	≥ 2.3	80	0	4	160

*Given twice daily
**Based on trifluridine component

Dose Level	BSA (m^2)	Dose (mg)*	Number of tablets per dose		Total Daily Dose (mg)*
			15 mg**	20 mg**	
-1 (30 mg/m^2)	< 1.09	30	2	0	60
	1.09 – 1.24	35	1	1	70
	1.25 – 1.39	40	0	2	80

	1.4 – 1.54	45	3	0	90
	1.55 – 1.69	50	2	1	100
	1.7 – 1.94	55	1	2	110
	1.95 – 2.09	60	0	3	120
	2.1 – 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
-2 (25 mg/m^2)	<1.1	25***	2***	1***	50***
	1.1 – 1.29	30	2	0	60
	1.3 – 1.49	35	1	1	70
	1.5 – 1.69	40	0	2	80
	1.7 – 1.89	45	3	0	90
	1.9 – 2.09	50	2	1	100
	2.1 – 2.29	55	1	2	110
	≥ 2.3	60	0	3	120
-3 (20 mg/m^2)	<1.14	20	0	1	40
	1.14 – 1.34	25***	2***	1***	50***
	1.35 – 1.59	30	2	0	60
	1.6 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.1 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

*Given twice daily
**Based on trifluridine component

***For total daily dose of 50 mg; patients should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.

Dose Modifications:

Toxicity	Action
Hematologic	
Grade 3 thrombocytopenia (platelets 25 to < 50 x 10^9/L) OR Grade 4 thrombocytopenia or neutropenia (platelets < 25 x 10^9/L or ANC < 0.5 x 10^9/L) requiring a ≤ 1 week delay in start of next cycle	Hold*; restart next cycle at same dose level
Grade 4 thrombocytopenia or neutropenia (platelets < 25 x 10^9/L or ANC < 0.5 x 10^9/L) requiring a > 1 week delay in start of next cycle	Hold*; restart next cycle at ↓ one dose level
Febrile neutropenia	Hold*; restart next cycle at ↓ one dose level
Non-hematologic	
Grade 3 or 4 non-hematologic; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhea responding to antidiarrheal therapy	Hold*; restart next cycle at ↓ one dose level
Interstitial Lung Disease/Pneumonitis (treatment-related)	Hold and investigate. If confirmed, discontinue permanently
*Restart when platelets recovered to ≥ 75 x 10^9/L and ANC recovered to ≥ 1.5 x 10^9/L and non-hematological toxicities ≤ grade 1. Do not re-escalate dose after it has been reduced.	

<u>Hepatic Impairment</u>

Higher incidence of grade 3 or 4 hyperbilirubinemia was observed in patients with moderate hepatic impairment.

(Continued on next page)

Hepatic Impairment	Bilirubin		AST	Starting Dose
Mild	≤ ULN	and	> ULN	No adjustment required
	< 1 – 1.5 x ULN	and	Any	
Moderate	> 1.5 – 3 x ULN	and	Any	Not recommended for use
Severe	> 3 x ULN			

Renal Impairment

Patients with moderate renal impairment (creatinine clearance = 30 - 59 mL/min) had a higher incidence (difference of at least 5%) of ≥ grade 3 adverse events (hemoglobin and leukocytes decreases) and serious adverse events compared to patients with normal or mild renal impairment.

Creatinine Clearance (mL/min)	Starting Dose
≥ 60	No adjustment required
30 - 59	No adjustment required; monitor closely for hematological toxicity and dose adjust accordingly
15 - 29	

Dose Level	Starting Dose* (mg/m^2) BID
0	20
-1	15
-2	Discontinue

*Based on the trifluridine component

Dosage	BSA (m^2)	Dose (mg)*	Tablets per Dose		Total Daily Dose (mg)*
			15 mg**	20mg**	
20 mg/m^2	< 1.14	20	0	1	40
	1.14 to 1.34	25***	2 in the evening***	1 in the morning***	50***

		1.35 to 1.59	30	2	0	60
		1.6 to 1.94	35	1	1	70
		1.95 to 2.09	40	0	2	80
		2.1 to 2.34	45	3	0	90
		≥ 2.35	50	2	1	100
	15 mg/m^2	< 1.15	15	1	0	30
		1.15 to 1.49	20	0	1	40
		1.5 to 1.84	25***	2 in the evening***	1 in the morning***	50***
		1.85 to 2.09	30	2	0	60
		2.1 to 2.34	35	1	1	70
		≥ 2.35	40	0	2	80
	*Given twice daily **Based on trifluridine component ***For total daily dose of 50 mg; patients should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.					
< 15 (End Stage Renal Disease)	Not studied, no data available					

Dosage in the Elderly

No adjustments of starting dose needed. No overall differences in effectiveness were reported based on age (≥65 years of age versus <65 years); higher incidences of severe myelosuppression were observed in patients aged ≥ 65 compared with those < 65. Efficacy and safety data in patients ≥ 75 years old is limited.

Dosage based on ethnicity description

No dose adjustments required. Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been rarely observed in one clinical trial of Asian patients as well as post marketing. There is limited data in African American patients.

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F - Adverse Effects

Refer to trifluridine / tipiracil drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting	• Anorexia / ↓ appetite • Fatigue • Diarrhea	• Venous thromboembolism • Interstitial lung disease / Pneumonitis

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G - Interactions

Refer to trifluridine / tipiracil drug monograph(s) for additional details.

- Monitor for decreased efficacy of human thymidine kinase substrates (e.g. zidovudine), consider switching to alternative antiviral that is not a human thymidine kinase substrate (e.g. lamivudine, abacavir, etc).

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H - Drug Administration and Special Precautions

Refer to trifluridine / tipiracil drug monograph(s) for additional details.

Administration

- Trifluridine / tipiracil should be given orally with a glass of water, within one hour of completion of morning and evening meals.
- If a dose is missed or held, the patient should not make up for the missed dose.
- Store at room temperature (15 - 30°C) in its original packaging.

Contraindications

- Patients who have a known hypersensitivity to the drug or to any of its excipients

Warnings/Precautions

- Contains lactose; carefully consider use in patients with hereditary lactase, glucose or galactose disorders.
- Use with caution in patients who received prior radiotherapy; may be at higher risk of hematological adverse effects.

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 **1 day** after the last dose.
- Fertility effects: Unlikely

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline, before each cycle and at each visit (including Day 15)

  Renal function tests; Baseline and at each visit

  Liver function tests; Baseline and at each visit

Proteinuria (by dipstick); Baseline and as clinically indicated

Clinical toxicity assessment for infection, bleeding, venous thromboembolism, GI and respiratory effects; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Trifluridine / tipiracil drug monograph, Ontario Health (Cancer Care Ontario).

Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiricil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:1437-48.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

November 2022 Added PEBC guideline link

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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