

# Gastric Cancer

Effective Date: April, 2021



## Background

The recognized risks factors for gastric cancer include male gender, older age, chronic inflammation (e.g.: *Helicobacter pylori* infection, intestinal metaplasia, pernicious anemia), cigarette smoking, obesity, and certain hereditary conditions (e.g. familial adenomatous polyposis).

Prognosis depends upon the stage at diagnosis; that is, prognosis is better with less penetration of tumour into the stomach wall, fewer involved regional lymph nodes, and no evidence of metastatic disease.

A multidisciplinary team is required to define and provide the optimal care for a patient with gastric carcinoma. It should be composed of thoracic and general surgeons, gastroenterologists, and oncologists.

Early involvement of a dietician is recommended to complete a nutritional assessment and to optimize the patient's nutritional status.

This guideline was developed to outline the management recommendations for adult patients with gastric cancer.

## Guideline Questions

1. What are the recommendations for the diagnostic workup of adult patients with gastric cancer?
2. What are the treatment recommendations for adult patients with gastric cancer?

## Search Strategy

The pubmed database was used with the following search criteria ("stomach neoplasms"[MeSH Terms] OR ("stomach"[All Fields] AND "neoplasms"[All Fields]) OR "stomach neoplasms"[All Fields] OR ("gastric"[All Fields] AND "cancer"[All Fields]) OR "gastric cancer"[All Fields]) AND (Clinical Trial, Phase III[ptyp] AND ("2018/01/01"[PDAT] : "2020/12/31"[PDAT])).

## Target Population

Adult ( $\geq 18$  years of age) patients with a confirmed or suspected diagnosis of gastric cancer.

## Recommendations

### Suggested Diagnostic Work-Up

- i. A complete endoscopic and radiologic evaluation is required to allow the multidisciplinary team to define the optimal management plan.
- ii. Esophagogastroduodenoscopy helps to distinguish between a gastric cancer that extends into esophagus and an esophageal cancer that extends into stomach. It also obtains a biopsy of the intraluminal mass to confirm the histologic diagnosis.

- iii. CT scan of the thorax abdomen, and pelvis should be performed at baseline and should be repeated prior to surgery if patients receive neoadjuvant therapy.
- iv. For gastric cancer patients, a PET CT can be considered for locally advanced cancers (for example node positive). PET CT may have limited utility in mucinous or diffuse tumours and does not replace a laparoscopic assessment for peritoneal disease.<sup>40</sup>
- v. If no metastases are seen on baseline imaging, a laparoscopic evaluation for peritoneal metastasis should be considered prior to surgical resection. Laparoscopic evaluation can alter management in up to 44% of cases.<sup>1</sup>
- vi. Bone scans can be done for patients suspected of having bone metastases, CT head or MRI for patients suspected of having brain metastases.
- vii. For patients on palliative systemic treatment, CT chest, abdomen, pelvis should be done every 2-3 months.
- viii. Individualized discussion regarding imaging after definitive chemoRT or after surgical resection for non-metastatic patients.
- ix. Perioperative chemotherapy should be considered for curative intent cases. Surgical resection should be with oncologic principles. A minimum D<sub>1</sub> resection by an experienced surgeon with a goal of 16 or more lymph nodes examined should be performed.
- x. Mismatch repair (MMR) or microsatellite instability (MSI) testing should be considered for curative intent cases. Retrospective analyses, and an individual patient meta-analysis of 1156 patients from 4 randomized trials (MAGIC, CLASSIC, ARTIST, and ITACA-S), identified 121 (7.8%) patients that were MSI high. MSI-high patients had better 5 year DFS (71.8 vs 52.3%, HR 1.88, 95% CI 1.28-2.76, p<0.01) and OS (77.5 vs 59.3%, HR 1.78, 95% CI 1.17-2.73, p 0.008), and did not seem to benefit from chemotherapy with 5 year DFS 70 vs 77% HR, 1.27; 95% CI, 0.53 to 3.04), and the 5-year OS was 75% versus 83% (HR, 1.50; 95% CI, 0.55 to 4.12).<sup>2</sup> MMR status may influence decisions regarding adjuvant and neoadjuvant chemotherapy for gastric cancer. Currently, the preferred neoadjuvant regimen is FLOT. A retrospective review of 101 patients, including 5 MSI-H patients treated with FLOT, demonstrated a relatively poor histological response to neoadjuvant therapy but a significantly superior overall survival for MSI-H versus MSS tumors.<sup>3</sup> Given the limited data available using the FLOT regimen, the applicability of using MSI testing is less clear.
- xi. Early involvement with a registered dietician, experienced with gastric cancer is recommended to support the unique nutritional needs of this patient population, particularly in the setting of surgery and/or significant >10% weight loss.

### **Stage Information:**

#### **Note:**

*Tumors involving the esophagogastric junction (EGJ) with the tumor epicenter no more than 2 cm into the proximal stomach are staged as esophageal rather than gastric cancers (refer to esophageal cancer guideline). In contrast, EGJ tumors with their epicenter located more than 2 cm into the proximal stomach are staged as stomach cancers.*

**Table 1. AJCC Cancer Clinical Staging System for Gastric Cancer, Eighth Edition.**

Stage	Depth of Tumour Penetration		Regional Node Involvement**		Metastases	
Stage 0	Tis	Carcinoma <i>in situ</i>	N0	None	M0	Absent
Stage Ia	T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa	N0	None	M0	Absent
Stage Ib	T1	As described above	N1	Metastases in 1 or 2 regional lymph nodes	M0	Absent
	T2	Tumor invades the muscularis propria*	N0	None	M0	Absent
Stage IIA	T1	As described above	N2	Metastases in 3 to 6 regional lymph nodes	M0	Absent
	T2	As described above	N1	As described above	M0	Absent
	T3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures **/**	N0	As described above		
Stage IIB	T1	As described above	N3a	Metastases in 7 to 15 regional lymph nodes	M0	Absent
	T2	As described above	N2	As described above	M0	Absent
	T3	As described above	N1	As described above	M0	Absent
	T4a	Tumor invades the serosa (visceral peritoneum)	N0	None	M0	Absent
Stage IIIa	T2	As described above	N3a	As described above	M0	Absent
	T3	As described above	N2	As described above	M0	Absent
	T4a	As described above	N1-2	As described above	M0	Absent
	T4b	Tumor invades adjacent structures/organs	N0	As described above	M0	Absent
Stage IIIb	T1-2	As described above	N3b	Metastases ≥16 regional lymph nodes	M0	Absent
	T3-4a	As described above	N3a	As described above	M0	Absent
	T4b	As described above	N1-2	As described above	M0	Absent
Stage IIIc	T3-4a	As described above	N3b	As described above	M0	Absent
	T4b	As described above	N3a-3b	As described above	M0	Absent
Stage IV	T <sub>any</sub>	As described above	N1-3	As described above	M <sub>1</sub>	Present

\* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.

\*\*The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

\*\*\*Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure, but is classified using the depth of the greatest invasion in any of these sites.

## Goals of Therapy

To render the patient free of disease, delay or prevent recurrence, and to improve or prolong survival. In patients that cannot be rendered disease free, prolong survival, palliate symptoms and maximize quality of life.

## Treatment Recommendations

Consider treatment on a clinical trial, if available.

See the Treatment Flow Chart found here:

<https://www.albertahealthservices.ca/info/cancerguidelines.aspx>

## Stage Ia

- i. Perform surgical resection with oncologic principles (minimum D1 resection by an experienced surgeon with a goal of 16 or more lymph nodes).
- ii. No adjuvant local or systemic therapy is indicated.

## Stage Ib-IIIc

- i. Surgery should be performed with oncologic principles (minimum D1 resection by an experienced surgeon with a goal of 16 or more lymph nodes examined).

Peri-operative chemotherapy should be considered in patients with clinical T2 or node positive disease prior to surgical resection (see below).

### Peri-Operative Chemotherapy:<sup>11</sup>

Note: According to the CRITICS trial, in patients who have received pre-operative chemotherapy, there is no evidence to suggest that further intensification of post-operative treatment with chemoradiation has any benefit.<sup>4</sup>

### *Preferred*

**FLOT** was shown to be superior to ECF/ECX in preliminary reports from the FLOT4-AIO phase III trial in terms of median overall survival (50 months vs. 35 months, HR:0.77,  $p=0.012$ ), and progression-free survival (30 months vs 18 months, HR:0.75,  $p=0.004$ ), and should therefore be considered standard of care.<sup>12</sup> [Level of evidence: I]

- i. Prophylactic GCSF should be considered for patients undergoing FLOT, as grade 3/4 neutropenia occurs at a higher rate than ECF/ECX.

### *Alternative Protocols (ECX/ECF/MAGIC): for patients not eligible for FLOT*

- i. When compared to surgery alone in patients with good performance status (ECOG  $\leq 1$ ) and T<sub>2-4</sub>N<sub>0-3</sub>M<sub>0</sub> adenocarcinoma of the distal third of the esophagus, gastro-esophageal junction, or stomach, peri-operative chemotherapy improves the five-year progression-free (HR 0.66, CI<sub>95%</sub> 0.53-0.81,  $p < 0.001$ ) and overall survival (from 23.0% to 36.3%, HR 0.74, CI<sub>95%</sub> 0.59-0.93,  $p = 0.008$ ).<sup>14</sup> [Level of evidence: I]

- ii. Similarly, peri-operative Cisplatin + Fluorouracil the five-year disease-free survival (34% *versus* 19%, HR 0.65, CI<sub>95%</sub> 0.48-0.89,  $p = 0.003$ ), overall survival (38% *versus* 24%, HR 0.69, CI<sub>95%</sub> 0.50-0.95,  $p = 0.02$ ), and rate of curative resection (84% *versus* 73%,  $p = 0.04$ ).<sup>15</sup>

- iii. These regimens require placement of a central venous catheter (CVC), peripherally inserted central catheter (PICC line), or port.

- iv. For patients who decline a central line, based on extrapolation from the ST03 trial,<sup>16</sup> ECX would be a reasonable option. Consideration should be made to substitute infusional 5-Fluorouracil for the capecitabine component in patients with impaired gastric acid production (eg. post gastrectomy,

proton pump inhibitor)

**For patients not suitable for peri-operative chemotherapy:**

In patients who have not had pre-operative chemotherapy, treatment options include adjuvant chemoradiation or chemotherapy. The decision between the two approaches benefits from multidisciplinary discussion.(see below).

**Adjuvant Chemoradiation:<sup>5</sup>**

i.Leucovorin followed by 5-Fluorouracil combined with radiotherapy.<sup>6</sup> [Level of evidence: I] Improves five-year relapse-free survival from 22% to 40% (HR 1.51, CI<sub>95%</sub> 1.25-1.83, *p* < 0.001) and five-year overall survival from 26% to 40% (HR 1.32, CI<sub>95%</sub> 1.10-1.60, *p* = 0.0046) when compared with surgery alone.

**Table 2.** Adjuvant Chemoradiation Schedule.

Cycle	Weeks	Therapy	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday/ Sunday	
Cycle 1	1	CT	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	—	—
	2-4	None	—	—	—	—	—	—	—
Cycle 2	1	CT RT	400 mg/m <sup>2</sup> 180 cGy	400 mg/m <sup>2</sup> 180 cGy	400 mg/m <sup>2</sup> 180 cGy	400 mg/m <sup>2</sup> 180 cGy	— 180 cGy	—	—
	2	RT	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	—	—
	3	RT	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	—	—
	4	RT	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	—	—
Cycle 3	1	CT RT	— 180 cGy	— 180 cGy	400 mg/m <sup>2</sup> 180 cGy	400 mg/m <sup>2</sup> 180 cGy	400 mg/m <sup>2</sup> 180 cGy	—	—
	2-4	None	—	—	—	—	—	—	—
Cycle 4	1	CT	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	—	—
	2-4	None	—	—	—	—	—	—	—
Cycle 5	1	CT	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	425 mg/m <sup>2</sup>	—	—
	2-4	None	—	—	—	—	—	—	—

CT = Chemotherapy (Leucovorin 20 mg/m<sup>2</sup> IV followed by 5-Fluorouracil 425 or 400 mg/m<sup>2</sup> IV)  
RT = Radiation (4,500 cGy over twenty-five fractions)

**Adjuvant Chemotherapy:**

For patients who have had an adequate lymph node dissection, particularly a D2 resection, without pre-operative treatment, adjuvant chemotherapy alone can be considered. It may also be considered in patients ineligible for adjuvant radiation. Treatment options include:

- i. Leucovorin + 5-Fluorouracil (de Gramont regimen used in the ITACA-S trial) Demonstrated a 5 year DFS of 44.6% and OS of 50.6%, which was not statically different from the more intensive FOLFIRI, Docetaxel/Cisplatin regimen.<sup>7</sup> [Level of evidence: I]
- ii. The ARTIST regimen: Capecitabine+ Cisplatin. The 3-year DFS was 74.2% in the chemotherapy arm.<sup>8</sup> [Level of evidence: I]
- iii. The CLASSIC regimen: Capecitabine + Oxaliplatin demonstrated 5-year disease free survival rate of 68% compared to 53% with surgery alone (HR 0.58, CI<sub>95%</sub> 0.47-0.72,  $p < 0.001$ ).<sup>9</sup> [Level of evidence: I]

### **Adjuvant chemoradiation versus Adjuvant chemotherapy:**

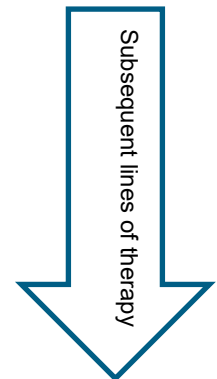
*Consider adjuvant chemoradiation for patients with 15 or fewer lymph nodes resected or with an R1 resection (microscopically positive margins).* The benefit of chemoradiation over chemotherapy has not been demonstrated after a D2 resection. A multidisciplinary discussion will help guide treatment selection. The ARTIST clinical trial randomized patients after a D2 lymph node resection, to receive chemoradiation (Capecitabine + Cisplatin + radiation) compared to chemotherapy alone (Capecitabine + Cisplatin). It did not demonstrate a clear benefit of chemoradiation, with 3 year DFS 78.2% vs 74.2%  $p=0.0862$ . In a hypothesis generating post hoc subgroup analysis, patients with node positive disease appeared to have a benefit from chemoradiation (3 year DFS 77.5% vs 72.3%, adjusted HR 0.6865; 95% CI, 0.4735 to 0.9952;  $P = .0471$ ). The ARTIST 2 clinical trial, randomized node positive, D2 resected gastric cancer patients to S-1, S-1 plus oxaliplatin, or radiation with S-1 /oxaliplatin was closed early due to futility. Preliminary data on the first 538 patients showed no significant benefit for the addition of radiation, and the S-1 arm had inferior outcomes to the oxaliplatin arm.

54% of patients in the Macdonald (Intergroup 0116) chemoradiation study received less than a D1 lymph node resection, with only 36% having had a D1 resection and 9.6% D2, suggesting that chemoradiation may be most beneficial in the context of an inadequate lymph node dissection.<sup>10</sup> CALGB 80101 randomized patients with resected gastric or EGJ tumors to adjuvant bolus 5FU and leucovorin or ECF, both arms received concurrent 5FU chemoradiation. Intensification of adjuvant chemotherapy with ECF did not significantly improve overall survival compared to adjuvant 5FU. A retrospective comparison of the Dutch D1D2 trial suggested significant improvements in overall survival and reduced local recurrence rates with the use of chemoradiation after an R1 resection, which is supported by other retrospective series.<sup>38,39</sup>

## Stage IV

**Table 3.** Summary of treatment options for stage IV gastric cancer.

HER2 Normal	HER2 Positive
FOLFOX/CAPOX or FOLFIRI (or Cisplatin/fluoropyrimidine[ <a href="#">Link</a> ])	Fluoropyrimidine, Cisplatin and Trastuzumab
Paclitaxel +/- Ramucirumab Prior Platinum: Irinotecan or FOLFIRI Prior FOLFIRI: Fluoropyrimidine & Platinum Docetaxel	
Trifluridine Tipiracil	



Unfunded: First line Nivolumab with FOLFOX/CAPOX CPS $\geq$ 5\*

### Stage IV (First Line)

- i. Palliative maneuvers to maintain and/or improve quality of life are indicated (e.g.: stent placement or radiotherapy to relieve dysphagia, pain, obstruction, or bleeding).
- ii. Palliative chemotherapy regimens<sup>17,18</sup> are generally continued as long as tumour shrinkage or stability is confirmed, as long as the side effects remain manageable, as long as the patient wishes to continue, and as long as the treatment remains medically reasonable.
- iii. Consider an early referral to palliative care [[link](#)].
- iv. In those patients with unresectable disease, consider early referral to dietician and psychosocial oncology.<sup>45</sup>

### HER2 Normal:

*Preferred Oxaliplatin/fluoropyrimidine or FOLFIRI [Level of evidence: I]*

- i. A network meta-analysis of systemic therapy for advanced gastric cancer demonstrated that anthracycline triplet chemotherapy and docetaxel, cisplatin, fluorouracil (5FU) triplets showed no benefit over fluoropyrimidine (FP: 5-fluorouracil (5FU) or capecitabine) doublets for overall survival (OS) or progression-free survival (PFS), and increased toxicity was noted.<sup>19</sup>
- ii. A fluoropyrimidine doublet containing oxaliplatin or irinotecan significantly improved overall survival compared with a fluoropyrimidine plus cisplatin (for a fluoropyrimidine plus irinotecan, the HR for death was 0.85, 95% CI 0.71-0.99; for a fluoropyrimidine plus oxaliplatin, the HR was 0.83, 95% CI 0.71-0.98). The cisplatin-fluoropyrimidine doublet was also associated with more grade 3 or 4 toxicity.

### FOLFOX/CAPOX

Four phase III trials have compared oxaliplatin to cisplatin based regimens (including ECF) suggesting similar efficacy. A meta-analysis of the REAL-2 trial and two randomized phase II trials

\* Nivolumab is Health Canada approved, but not funded in Alberta for this indication.



comparing oxaliplatin to cisplatin based regimens demonstrated that oxaliplatin was associated with significant improvements in PFS (HR 0.88, 95% CI 0.80-0.98) and overall survival (HR for death 0.88, 95% CI 0.78-0.99), and with less neutropenia, anemia, alopecia, and thromboembolic events, but with more neurotoxicity and diarrhea.<sup>20-24</sup>

### *FOLFIRI*

- i. Suitable first or second line regimen for patients with an ECOG of 0-2: Irinotecan (180 mg/m<sup>2</sup> IV over ninety minutes) and Leucovorin (400 mg/m<sup>2</sup> IV over two hours) followed by 5-Fluorouracil (2400 mg/m<sup>2</sup> as 46 hour infusion) every 2 weeks.
- ii. FOLFIRI followed by ECX was compared to the reverse sequence in the first line setting of metastatic GE junction/gastric adenocarcinoma.<sup>25</sup> The dosing and duration of Capecitabine in the ECX arm (oral Capecitabine 1g/m<sup>2</sup> twice per day from day 2 to day 15 every 3 weeks) was different than in the REAL-2 trial.
- iii. FOLFIRI followed by ECX was superior to the reverse strategy for the primary endpoint of time to treatment failure (5.08 months versus 4.24 months, HR 0.77, CI95% 0.63-0.83, p = 0.008), however, OS (9.5 months versus 9.7 months; p=0.95) and PFS (5.3 months versus 5.8 months; p=0.96) were similar between the two sequences.
- iv. Patients who received first line ECX had higher rates of grade 3/4 toxicities, especially hematological ones.

### *Nivolumab with FOLFOX/CAPOX CPS≥5*

- i. In the ATTRACTION-4 study<sup>41</sup> patients in Japan, Korea or Taiwan were randomized to nivolumab or placebo with chemotherapy (SOX or CapeOx). In this study with dual primary endpoints, the nivolumab + chemotherapy patients had improved progression free survival (median PFS 10.45 months versus 8.34 months with chemotherapy alone (HR: 0.68, 95%CI: 0.51-0.90, p<0.001). However, there was no improvement in overall survival.
- ii. The Checkmate 649 study<sup>42</sup> study was an international trial (including populations from Asia, North America and the rest of the world) which randomized patients to nivolumab with chemotherapy (Nivolumab + XELOX or Nivolumab + FOLFOX) or chemotherapy alone (XELOX or FOLFOX). This study demonstrated a statistically significant improvement in overall survival in patients with the addition of nivolumab in the PD-L1 CPS≥5 (median OS 14.4 months versus 11.1 months in the chemotherapy alone arm; HR: 0.71, 95%CI: 0.59-0.86, p<0.001). Furthermore, OS benefit was also seen in the secondary endpoints analyzing patients with PD-L1 CPS≥1 as well as in all randomized patients. Similarly, benefits were seen in PFS, overall responses and duration of response in the patients receiving nivolumab<sup>†</sup>.

### *Pembrolizumab*

- i. In the phase III KEYNOTE-062 trial, 763 patients with previously untreated advanced gastric or GE junction adenocarcinoma patients with a CPS ≥ 1 were randomized to pembrolizumab, chemotherapy

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<sup>†</sup> Nivolumab is Health Canada approved, but not funded in Alberta for this indication.

(cisplatin plus a fluoropyrimidine) or combined therapy. Pembrolizumab was non-inferior to chemotherapy alone for overall survival. In an exploratory analysis of patients with a CPS  $\geq$  10, there was a clinically meaningful improvement in median overall survival with pembrolizumab compared to chemotherapy alone (17.4 vs 10.8 months, HR 0.69, 95% CI 0.49-0.97). Pembrolizumab is not currently funded.

ii. At this time, the addition of pembrolizumab to chemotherapy has not demonstrated sufficient improvement in outcomes to justify the associated toxicities.<sup>43</sup>

#### *Palliative Chemotherapy Options (Established in the REAL-2 Clinical Trial) include*

Triplet regimens with anthracyclines are historically considered as options, but no longer preferred due to increased rates of toxicity, without clear improvements in PFS or OS.<sup>19</sup>

#### **Capecitabine-based Combination Regimens:**

i. Capecitabine-based combination regimens (e.g.: ECX, EOX, CX) offer a superior response rate (45.6% versus 38.4%, OR 1.38, CI95% 1.10-1.73,  $p = 0.006$ ) and overall survival (HR 0.87, CI95% 0.77-0.98,  $p = 0.02$ ) when compared to 5-Fluorouracil-based combination chemotherapies (e.g.: ECF, EOF, CF).<sup>26</sup>

ii. Oxaliplatin is the preferred platinum as it reduces the risk of death (HR 0.88, CI95% 0.78-0.99,  $p = 0.04$ ), progression (HR 0.88, CI95% 0.80-0.98,  $p = 0.02$ ), and thromboembolism.<sup>23,27</sup>

#### **HER2 Positive:**

i. HER2 over-expression can be demonstrated in 16% of gastric cancers. The addition of Trastuzumab to Cisplatin plus either Capecitabine or 5-Fluorouracil was associated with a superior progression-free (6.7 months versus 5.5 months, HR 0.71, CI95% 0.59-0.85,  $p = 0.0002$ ) and overall survival (13.8 months versus 11.1 months, HR 0.74, CI95% 0.60-0.91,  $p = 0.0046$ ).<sup>28</sup> In a pre-planned exploratory analysis, the subset of patients with high-level HER2 expression (immunohistochemistry scores (IHC) of 2+ with FISH positivity or IHC3+) achieved a median overall survival of 16.0 months. [Level of evidence: I] In the updated survival analysis, the median overall survival for the addition of trastuzumab was 13.1 months as compared to 11.7 months for the chemotherapy alone arm (HR 0.80, CI95% 0.67- 0.91). In the updated pre-planned analysis[[link](#)], only the patients in the IHC3+ subgroup showed a statistically significant survival benefit (18.0 months vs 13.2 months, HR 0.66 (CI95% 0.50-0.87)). [Level of evidence:1]

#### *Contraindications to platinum/fluoropyrimidine or FOLFIRI*

In patients who have a contraindication to a platinum/fluoropyrimidine combination, or FOLFIRI, the following regimen may be considered as an alternative but it does not have the same degree of survival benefit:

##### **a. ELF<sup>29</sup>**

## Stage IV (Second Line)

### Combination Systemic Therapy:

i. In patients with a preserved performance status, modest benefits have been achieved with second-line chemotherapy. For patients who are fit enough, combination systemic therapy should be considered. Options include:

a. Paclitaxel + Ramucirumab

1. Compared to Paclitaxel alone, in patients with ECOG 0-1 the addition of Ramucirumab significantly improved overall survival (7.6 months *versus* 9.6 months, HR 0.807, CI<sub>95%</sub> 0.678-0.962,  $p = 0.017$ )<sup>30</sup> [Level of evidence: I]

2. Similar time to deterioration in performance status was reported in the paclitaxel arm and the paclitaxel plus ramucirumab arm ( $p=0.0941$ ) according to QLQ-C30 scales. EQ-5D scores were comparable between treatment arms, stable during treatment, and worsened at discontinuation.<sup>25,31</sup>

b. FOLFIRI as above can be considered in the second line setting, after a fluoropyrimidine/platinum combination.<sup>25</sup> It is unclear as to whether the addition of 5-fluorouracil to irinotecan confers additional benefit and consideration can be single agent irinotecan (see below).

c. A fluoropyrimidine/platinum combination such as FOLFOX or CAPOX can be considered in the second line setting after FOLFIRI.<sup>25</sup> While combinations like ECX, EOX, ECF or EOF have more direct evidence in this setting, it is reasonable to omit the anthracycline in the second line setting due to the added toxicities and lack of increased efficacy observed in the first line setting.<sup>19,25</sup>

### Single Agent Systemic Therapy:

i. Paclitaxel [Level of evidence: I]

a. Paclitaxel is equivalent to Irinotecan every 2 weeks<sup>32</sup> in terms of median overall survival (8.4 months for Irinotecan *versus* 9.5 months for Paclitaxel, HR 1.132, CI<sub>95%</sub> 0.86-1.49,  $p = 0.38$ ); median progression-free survival (2.3 months for Irinotecan and 3.6 months for Paclitaxel, HR 1.14, CI<sub>95%</sub> 0.88-1.49,  $p = 0.33$ ); and overall response rate (13.6% for Irinotecan and 20.9% for Paclitaxel,  $p = 0.20$ ). However, Paclitaxel confers less grade 3/4 neutropenia (28.7% *versus* 39.1%), anemia (21.3% *versus* 30.0%), anorexia (7.4% *versus* 17.3%), and fatigue (6.5% *versus* 12.7%).

ii. Irinotecan [Level of evidence: I]

a. Irinotecan 250 to 350 mg/m<sup>2</sup> IV three weeks demonstrated a median overall survival of 4.0 months *versus* 2.4 months, (HR 0.48, CI<sub>95%</sub> 0.25-0.92,  $p = 0.012$ ) compared to best supportive care.<sup>33</sup>

b. Irinotecan 150 mg/m<sup>2</sup> IV every two weeks (or Docetaxel) demonstrated a median overall survival of 5.3 months *versus* 3.8 months, HR 0.657, CI<sub>95%</sub> 0.485-0.891,  $p = 0.007$  compared to best supportive care.<sup>34</sup>

iii. Docetaxel [Level of evidence: I]

a. Docetaxel 60 mg/m<sup>2</sup> IV every three weeks or Irinotecan improves overall survival when

compared with best supportive care (5.3 months *versus* 3.8 months, HR 0.657, CI<sub>95%</sub> 0.485-0.891,  $p = 0.007$ ).<sup>34</sup>

**b.** Docetaxel 75 mg/m<sup>2</sup> IV every three weeks improves overall survival (5.2 months *versus* 3.6 months, HR 0.67, CI<sub>95%</sub> 0.49-0.92,  $p = 0.01$ ) and pain scores when compared with best supportive care.<sup>35</sup>

**iv. Ramucirumab [Level of evidence: I]**

**a.** This improved overall survival when compared to best supportive care (5.2 versus 3.8 months, multivariable HR 0.774, CI<sub>95%</sub> 0.605-0.991,  $p = 0.042$ ) with no difference in quality of life scores at 6 weeks.<sup>36</sup> Patients enrolled in the study had an ECOG 0-1 and Ramucirumab was also associated with a delay to median time to deterioration of performance status. Ramucirumab is not currently funded for single agent use.

**Stage IV (Third or Greater Line)**

**i. TAS-102**

**a.** TAS-102 (Trifluridine/tipiracil)[Level of evidence: I]

**b.** In patients with an ECOG 0-1 who had received 2 or more lines of systemic therapy, TAS-102 demonstrated an improvement in median overall survival to 5.7 months from 3.6 months, compared to placebo (HR 0.69, CI<sub>95%</sub> 0.56-0.85,  $p = 0.00029$ , two-sided  $p=0.00058$ ).<sup>37</sup>

**c.** Higher rates of grade 3 or higher were observed with TAS-102 in terms of neutropenia (n=114, 35=4%) and anemia (n=64, 19%), while with placebo abdominal pain (n=15, 9%) and general deterioration of physical health (n=15, 9%) were more common. No differences were seen in quality of life between patients treated with TAS-102 and placebo.<sup>‡</sup>

**ii. Nivolumab<sup>§</sup>**

**a.** The ATTRACTION-2<sup>44</sup> study randomized patients with advanced gastric or GEJ cancer who were refractory or intolerant to two or more previous lines of chemotherapy and naive to PD-1 therapy or other pharmacotherapies for the regulation of T-cells to randomly receive nivolumab or placebo. Median overall survival was improved in the nivolumab group as compared to the placebo group (5.26 months versus 4.14 months, HR 0.63, 95%CI: 0.51-0.78,  $p<0.001$ ).

**b.** Nivolumab is not currently available on the Alberta CancerCare Drug Benefit List for this indication

**c.** At this time, the Alberta GI Tumour Group does not support the routine use of nivolumab in this setting. At this point the clinical benefit may not outweigh the associated toxicities.

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<sup>§</sup> Nivolumab is not funded in Alberta for this indication.

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## Appendix A: Chemotherapy Regimens

Regimen	Description
Perioperative FLOT	4-cycles prior to surgery, with a further 4 cycles post-surgery. Each cycle lasts 14 days and consists of 5-FU 2600 mg/m <sup>2</sup> (24 h) day 1 and leucovorin 200 mg/m <sup>2</sup> (2h), day 1 and oxaliplatin 85 mg/m <sup>2</sup> (2 h) day 1 and docetaxel 50 mg/m <sup>2</sup> (1 h), every 2 weeks.
Perioperative ECX/ECF/MAGIC	3-cycles prior to surgery, with a further 3 cycles post-surgery. three-week cycles of Epirubicin 50 mg/m <sup>2</sup> and Cisplatin 60 mg/m <sup>2</sup> IV on day one plus a continuous IV infusion of 5-Fluorouracil 200 mg/m <sup>2</sup> /day over twenty-one days.
Perioperative Cisplatin + Fluorouracil	Six four-week peri-operative cycles of Cisplatin 100 mg/m <sup>2</sup> IV on day one plus 5-Fluorouracil 800 mg/m <sup>2</sup> /day over days one through five days
Adjuvant Leucovorin + 5-Fluorouracil + RT	Five four-week cycles where Leucovorin (20 mg/m <sup>2</sup> IV) followed by 5-Fluorouracil (425 mg/m <sup>2</sup> IV) is administered daily on the first five consecutive days of cycles one, four, and five. During cycles two and three, radiotherapy is administered on weekdays for twenty-five fractions (180 cGy per fraction). Leucovorin (20 mg/m <sup>2</sup> IV) followed by 5-Fluorouracil (400 mg/m <sup>2</sup> IV) is administered daily on the first four and last three days of radiotherapy (see grid below).
Adjuvant Leucovorin + 5-Fluorouracil (de Gramont)	Nine cycles of Leucovorin 100 mg/m <sup>2</sup> IV over 2 hours on days 1–2 and 5-Fluorouracil 400 mg/m <sup>2</sup> as bolus followed by daily 22 hour infusion of 600 mg/m <sup>2</sup> every 14 days
Adjuvant Capecitabine + Cisplatin (ARTIST)	Six cycles of the Capecitabine 1,000 mg/m <sup>2</sup> twice daily on days 1 to 14 and Cisplatin 60 mg/m <sup>2</sup> on day 1 every 3 weeks
Adjuvant Capecitabine + Oxaliplatin (CLASSIC)	Eight cycles of Capecitabine 1,000 mg/m <sup>2</sup> twice daily on days 1 to 14 and Oxaliplatin 130 mg/m <sup>2</sup> on day 1 every 3 weeks
Adjuvant Capecitabine + Cisplatin + RT (ARTIST)	Two cycles of Capecitabine/Cisplatin followed by 45-Gy chemoradiation with capecitabine 1,650 mg/m <sup>2</sup> per day for 5 weeks, followed by two more cycles of Capecitabine/Cisplatin
Nivolumab + SOX (ATTRACTION-4)	Nivolumab (360 mg intravenously every 3 weeks) plus SOX (S-1, 40 mg/m <sup>2</sup> orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m <sup>2</sup> intravenously on day 1 every 3 weeks)
Nivolumab + CapeOx (ATTRACTION-4)	Nivolumab (360 mg intravenously every 3 weeks) plus CapeOX (capecitabine, 1000 mg/m <sup>2</sup> orally twice daily for 14 days followed by 7 days off; oxaliplatin, 130 mg/m <sup>2</sup> intravenously on day 1 every 3 weeks)
Nivolumab + XELOX (Checkmate 649)	Nivolumab 360mg IV + XELOX (intravenous oxaliplatin 130 mg/m <sup>2</sup> ) (day 1) followed by oral capecitabine 1,000 mg/m <sup>2</sup> twice daily (day 1, evening, to day 15, morning)q 3 weekly
Nivolumab + FOLFOX (Checkmate 649)	Nivolumab 240mg + FOLFOX (oxaliplatin 85 mg/m <sup>2</sup> IV infusion on day 1, then leucovorin 400 mg/m <sup>2</sup> IV infusion, plus 5-FU 400 mg/m <sup>2</sup> IV bolus on day 1, then 1200 mg/m <sup>2</sup> /day for 2 d (total 2400 mg/m <sup>2</sup> over 46-48 h) q2 weekly
ECX	Epirubicin (50 mg/m <sup>2</sup> IV over twenty minutes) and Cisplatin (60 mg/m <sup>2</sup> IV over one hour) are administered on day one, and Capecitabine 625 mg/m <sup>2</sup> PO Q12h is administered for twenty-one consecutive days.
EOX	Epirubicin (50 mg/m <sup>2</sup> IV over twenty minutes) and Oxaliplatin (130 mg/m <sup>2</sup> IV over two to five hours) are administered on day one, and Capecitabine 625 mg/m <sup>2</sup> PO Q12h is administered for twenty-one consecutive days.
ECF	Epirubicin (50 mg/m <sup>2</sup> IV over twenty minutes) and Cisplatin (60 mg/m <sup>2</sup> IV over one hour) administered on day one, and 5-Fluorouracil (200 mg/m <sup>2</sup> /day)



Regimen	Description
EOF	Epirubicin (50 mg/m <sup>2</sup> IV over twenty minutes) and Oxaliplatin (130 mg/m <sup>2</sup> IV over two to five hours) administered on day one, and 5-Fluorouracil (200 mg/m <sup>2</sup> /day)
Trastuzumab + Cisplatin + Capecitabine (ToGA)	Trastuzumab (Initial loading dose 8 mg/kg i.v. infusion on Day 1 of cycle, followed by 6 mg/kg i.v. infusion every 3 weeks until disease progression) added to six three-week cycles of Cisplatin 80 mg/m <sup>2</sup> IV on day one plus Capecitabine 1,000 mg/m <sup>2</sup> po BID for fourteen days
Trastuzumab + Cisplatin + 5-Fluorouracil (ToGA)	Trastuzumab (Initial loading dose 8 mg/kg i.v. infusion on Day 1 of cycle, followed by 6 mg/kg i.v. infusion every 3 weeks until disease progression) added to six three-week cycles of Cisplatin 80 mg/m <sup>2</sup> IV on day one plus 5-Fluorouracil 800 mg/m <sup>2</sup> continuous IV infusion on days one through five
ELF	Three-week cycles where Etoposide (120 mg/m <sup>2</sup> IV), Leucovorin (300 mg/m <sup>2</sup> IV), and 5-Fluorouracil (500 mg/m <sup>2</sup> IV) are administered on days one, two, and three.
Paclitaxel + Ramucirumab (RAINBOW)	Paclitaxel 80 mg/m <sup>2</sup> on days 1, 8, 15 every 4 weeks with Ramucirumab 8 mg/kg IV days 1, 15
Single Agent Paclitaxel	Paclitaxel 80 mg/m <sup>2</sup> IV on days one, eight, and fifteen every four weeks
Single Agent Irinotecan	Irinotecan 250 to 350 mg/m <sup>2</sup> IV every three weeks or 150mg/m <sup>2</sup> IV every two weeks
Single Agent Docetaxel	Docetaxel 60 or 75 mg/m <sup>2</sup> IV every three weeks
Single Agent Ramucirumab	Ramucirumab 8mg/kg IV every 2 weeks
TAS-102	TAS-102 (Trifluridine/tipiracil) 35 mg/m <sup>2</sup> po twice daily on days 1-5 and days 8-12 every 28 days
Single Agent Nivolumab	Nivolumab (3mg/kg IV q 2 weekly)
FOLFIRI	Irinotecan (180 mg/m <sup>2</sup> IV over 90 minutes) concurrently with folinic acid (400 mg/m <sup>2</sup> [or 2 x 250 mg/m <sup>2</sup> ] IV over 120 minutes) followed by fluorouracil (400–500 mg/m <sup>2</sup> IV bolus) then fluorouracil (2400–3000 mg/m <sup>2</sup> intravenous infusion over 46 hours)
FOLFOX	FOLFOX (oxaliplatin 85 mg/m <sup>2</sup> IV infusion on day 1, then leucovorin 400 mg/m <sup>2</sup> IV infusion, plus 5-FU 400 mg/m <sup>2</sup> IV bolus on day 1, then 1200 mg/m <sup>2</sup> /day for 2 d (total 2400 mg/m <sup>2</sup> over 46-48 h) q2 weekly

## Development and Revision History

This guideline was reviewed and endorsed by the Alberta GI Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, gastroenterologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2010.

## Levels of Evidence

<b>I</b>	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
<b>II</b>	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
<b>III</b>	Prospective cohort studies
<b>IV</b>	Retrospective cohort studies or case-control studies
<b>V</b>	Studies without control group, case reports, expert opinion

## Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## Abbreviations

AHS, Alberta Health Services; CCA, CancerCare Alberta; DFS, disease free survival; OS, Overall Survival; MMR, Mismatch Repair; EGJ, Esophagogastric junction; CVC, Central Venous Catheter; PICC, Peripherally Inserted Central Catheter; IHC, Immunohistochemistry.

## Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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