Trastuzumab and FOLFOX-6 Modified Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with HER2 positive metastatic gastric or gastroesophageal junction cancer	C16	00704a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Trastuzumab is given by intravenous infusion at a dose of 6mg/kg on day 1 of cycle 1, followed by 4mg/kg from Cycle 2 onwards. Treatment is administered every 14 days until disease progression or unacceptable toxicity develops.

FOLFOX is administered every 14 days until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin order	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1	Trastuzumab	6mg/kg	IV infusion[a] Observe post infusion[b]	250ml 0.9% NaCl[c] over 90mins	Cycle 1 only
1	1	Trastuzumab	4mg/kg	IV infusion Observe post infusion[b]	250ml 0.9% [b]NaCl over 30 mins	**Every 14 days from cycle 2 onwards**
2	1	Oxaliplatin[d]	85mg/m^2	IV infusion	500ml glucose 5% over 2hrs	Every 14 days
3	1	Folinic Acid[e] (Calcium leucovorin)	400mg/m^2	IV infusion	250ml glucose 5% over 2hrs	Every 14 days
4	1	5-Fluorouracil[f]	400mg/m^2	IV bolus		Every 14 days
5	1	5-Fluorouracil[f]	2400mg/m^2	Continuous IV infusion	Over 46h in 0.9% NaCl	Every 14 days

[a]Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally.
Trastuzumab is administered subcutaneously at a dose of 600mg over 2-5minutes.
The injection site should be alternated between the left and right thigh.
New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard.
During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.

[b]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[c]Trastuzumab is incompatible with glucose solution.

[d] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline
For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction
Oxaliplatin administration must always precede the administration of 5-Fluorouracil.
Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.

[e]Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.
Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of fluorouracil.

[f]See dose modifications section for patients with identified partial DPD deficiency

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- HER2 overexpression as determined by an accurate and validated assay
- Adequate haematological, renal and liver status

CAUTION:

Use with caution in patients with

- Previous pelvic radiotherapy
- Baseline LVEF < 55% for trastuzumab therapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy

EXCLUSIONS:

- Hypersensitivity to trastuzumab, oxaliplatin, fluorouracil or any of the excipients
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months).
- Severe renal impairment (creatinine clearance < 30ml/min)
- Peripheral neuropathy with functional impairment prior to first cycle
- Known complete DPD deficiency
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Cardiac function (LVEF using ECHO or MUGA scan)
- ECG (if patient has compromised cardiac function)
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- Blood, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles
- Cardiac function, LFTs, creatinine every 12 weeks. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- **DPD deficiency:**
  - Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment.
  - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Trastuzumab

- None usually recommended. Discontinue if unacceptable toxicity occurs.
- If the patient misses a dose of trastuzumab by one week or less, then the usual maintenance dose of 4mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (6mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (4mg/kg) should then be given every 3 weeks from that point.

FOLFOX-6 modified

- The following dose reductions should be used when calculating FOLFOX dose reductions for patients with toxicities**.**

Table 1: Dose Reduction Levels for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus fluorouracil is delayed or omitted

Haematological:

Table 2. Dose Modifications for Haematological Toxicity (FOLFOX-6 modified)

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**ANC ($x\ 10^9$/L)**	**Oxaliplatin**	**Fluorouracil**
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • ANC ≥ 1.5 within 4 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	Maintain dose level
	4	<0.5	↓ 1 dose level	Omit bolus and ↓1 infusion dose level
	Grade	**Platelets ($x10^9$/L)**	**Oxaliplatin**	**Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • Platelets ≥ 75 within 4 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remains <75 after 4 weeks discontinue treatment	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

Renal and Hepatic Impairment:

Table 3: Recommended dose modifications in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Trastuzumab	No dedicated studies of trastuzumab in patients with renal impairment have been conducted. Based on a population pharmacokinetic (PK) analysis renal impairment was not shown to affect trastuzumab disposition		No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.			
Oxaliplatin	**CrCl (ml/min)**	**Dose**	Little information available. Probably no dose reduction necessary Clinical decision			
	≥30	Treat at normal dose and monitor renal function				
	<30	Contraindicated				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contraindicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity.			

Management of adverse events:

Table 4: Dose modification schedule for trastuzumab based on adverse events

Adverse reactions	Recommended dose modification
LVEF drops ≥ 10 ejection fraction points from baseline and to below 50%	Withhold treatment. Repeat LVEF after 3 weeks. No improvement or further decline consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure	Consider discontinuation – refer to cardiology for review. Clinical decision.
Grade 4 hypersensitivity reactions	Discontinue
Haematological	Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.

*NCI CTCAE Grading

Table 5: Dose modification schedule for (FOLFOX-6 modified) based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 • First occurrence • 2nd occurrence • Persistent Grade 4	 ↓ 1 dose level ↓1 dose level Discontinue oxaliplatin Discontinue oxaliplatin	Reduce oxaliplatin by 1 dose level
Laryngo-pharyngeal dysaesthesia		Increase infusion time from 2 to 6 hrs
Stomatitis		Delay treatment until stomatitis reaches level of grade 1 or less
Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates	Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.	

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re- challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

Table 6: Dose modification of Modified FOLFOX-6 for diarrhoea

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	Diarrhoea	Oxaliplatin	Fluorouracil
• If diarrhoea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. • If diarrhoea is less than Grade 2 within 4 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If diarrhoea remains greater than or equal to Grade 2 after 4 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level of IV push and infusional 5-fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 1 dose level of IV push and infusional 5-fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Trastuzumab: Minimal **(Refer to local policy).**
Oxaliplatin: Moderate (**Refer to local policy).**
5-fluorouracil: Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered.
Patient should be educated about the possibility of delayed infusion-related symptoms.

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil. Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.

Trastuzumab:

- **Cardiac toxicity**:
  - Trastuzumab has been associated with moderate to severe cardiac failure. Baseline and 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - If LVEF drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50 %, treatment should be withheld and a repeat LVEF assessment carried out within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
  - Trastuzumab and anthracyclines should not be given concurrently in combination due to cardiotoxicity risk.Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

- **Trastuzumab infusion-associated symptoms,** usually chills and fever may occur. Stop infusion and consider antihistamine cover. When symptoms have resolved the infusion may be recommenced. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
- **Pulmonary events:** Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These events may occur as part of an infusion-related reaction or with a delayed onset. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Oxaliplatin:

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
- **Haemolytic Ureamic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

5-Fluorouracil:

- **Hand-foot syndrome (HFS): HFS,** also known as palmar-plantar erythrodysaesthesia (PPE), has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.

DRUG INTERACTIONS:

- A possible interaction with warfarin and trastuzumab has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

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1	23/03/2022		Prof Maccon Keane
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.