Durvalumab FLOT (Fluorouracil, Oxaliplatin and Docetaxel)

Indication
Perioperative chemotherapy for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma.

ICD-10 codes
Codes with a prefix C15, C16

Regimen details
Durvalumab
Durvalumab 1500mg IV infusion given every 4 weeks

FLOT chemotherapy (given every 2 weeks)

Day	Drug	Dose	Route
1	Docetaxel	50 mg/m^2	IV infusion
1	Oxaliplatin	85 mg/m^2	IV infusion
1	Folinic acid	350mg	IV infusion
1 (24 hours)	Fluorouracil	2600 mg/m^2	24 hour IV infusion

Cycle frequency
Durvalumab is given every 4 weeks (i.e. every other cycle) with FLOT chemotherapy for 2 doses before surgery and for 2 doses after surgery and then continued every 4 weeks as a single agent for a further 10 cycles

FLOT is given every 2 weeks for 4 cycles before surgery and 4 cycles after surgery

Number of cycles
See above

Administration
Durvalumab is given in 100mL Sodium Chloride 0.9%. Administer the drug solution over 60 minutes using a volumetric pump through an in-line 0.2µm or 1.2µm polyethersulfone or 0.2µm positively charged nylon filter. Patients should be observed for signs and symptoms of infusion-related reactions. In the event of an infusion-related reaction, stop the infusion and administer corticosteroid and antihistamine. Seek medical advice. For grade 1 or 2 severity, subsequent doses may be considered using pre-medication. For grade 3 or 4 severity, discuss with consultant.

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes. Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Oxaliplatin is administered in 250mL glucose 5% over 2 hours. This is infused concurrently with leucovorin in 250mL glucose 5% over 2 hours. The line should then be flushed with glucose 5%. Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions.

Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device or as a continuous peripheral IV infusion in 1000mL sodium chloride 0.9%.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel or oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require

discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of treatment and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Pre-medication

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to docetaxel. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive premedication of Chlorphenamine 10mg IV and Ranitidine 50 mg IV 30 minutes prior to Oxaliplatin. Dexamethasone should be given as above.

Emetogenicity

This regimen has moderate-high emetic potential

Additional supportive medication

Mouthwashes as per local policy
H2 antagonist or proton-pump inhibitor if required Loperamide if required.
GCSF Days 3-7

Extravasation

Docetaxel and Oxaliplatin are exfoliant (Group 4)
Fluorouracil is an inflammatant (Group 2)
Durvalumab is neutral (Group 1)

Investigations – pre first cycle

Standard pre-SACT investigations, including DPYD testing and standard pre-Immunotherapy tests and ECG

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Iron studies	Pre cycle 4
Calcium	7 days
TFTs	7 days
Glucose	7 days
Cortisol	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L

Bilirubin	< ULN
ALT/AST	< 1.5 x ULN
Alkaline phosphatase	< 2.5 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min

Dose modifications

Do not amend the dose of durvalumab

Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

Immunotherapy toxicities should be aggressively managed as can cause permanent and life threatening complications.

Refer to UKONS and ESMO guidance for treatment of immune related toxicities.

Available at:

https://www.lancashireandsouthcumbria.icb.nhs.uk/our-work/canceralliance/information-professionals/clinical-reference-groups/acute-oncology-crg-metastatic-spinal-cord-compression-mscc-crg

- ### Haematological toxicity

Defer treatment for 1 week if neutrophil count <1.5 x 10^9/L and/or platelets < 100 x 10^9/L.

Toxicity	Occurrence	Docetaxel dose	Oxaliplatin dose	Fluorouracil dose
Neutrophils <1.5 x 10^9/L, febrile neutropenia* or neutrophils <0.5 x 10^9/L for > 7 days	1st	75%	100%	No change
	2nd	75%	75%	No change
	3rd	Stop treatment		
Platelets < 100 x 10^9/L	1st	Full dose	75%	75% dose
	2nd	75%	75%	75% dose
	3rd	Stop treatment		

If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce all subsequent doses of docetaxel to 75%, fluorouracil to 50% and oxaliplatin dose to 55mg/m^2.

- ### Renal impairment

CrCl (mL/min)	**Oxaliplatin dose**	**Fluorouracil dose**
≥ 50	100%	100%
30-49	50%	100%
10-29	Omit	30 - 50% dose reduction
< 10	Omit	50% dose reduction

There is no data available on the use of docetaxel in severe renal impairment. No modifications required.

- ### Hepatic impairment

Bilirubin (x ULN)		**AST/ALT (x ULN)**	**Docetaxel dose**	**Oxaliplatin dose**	**Fluorouracil dose**
≤ 1.5	and	≤ 1.5	100%	100%	100%
1.5 - 3	and	≤ 3	75%	100%	Consider dose reduction*
3 – 5	or	3 – 5	Discuss with consultant	50%	30% dose reduction*
> 5	or	> 5	Omit	omit	Contraindicated

*consultant decision

If bilirubin > ULN withhold dose (or consultant decision to treat)

- ### Other toxicities

For all toxicities, delay treatment until resolved to ≤ Grade 1. Then reduce doses as per the following tables:

Dose modification for Neurologic Toxicities for Oxaliplatin

Peripheral Neuropathy Grade*	**Dose Modification of oxaliplatin**
Grade 1	Maintain dose
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 65 mg/m2
Grade 3: paraesthesia first occurrence paraesthesia persisting until next cycle	Reduce dose to 65 mg/m2 Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin
Pharyngo-laryngeal dysethesia	Increase duration of infusion to 6 hours

Oxaliplatin and Fluorouracil

Toxicity	**Definition**	**Oxaliplatin dose**	**Fluorouracil dose**
Diarrhoea	Grade 2	100%	80%
	Grade 3	65mg/m^2	50%
	Grade 4	Discontinue treatment	
Stomatitis/Mucositis	Grade 2	100%	80%
	Grade 3	65mg/m^2	50%
	Grade 4	Discontinue treatment	
Palmar-Plantar erythema	Grade 2	100%	80%
	Grade 3/4	100%	50%
Peripheral neuropathy	Grade 2/3	65mg/m^2	100%
	Grade 4	Discontinue	100%

Docetaxel

Toxicity	**Definition**	**Docetaxel dose**
Peripheral neuropathy	Grade 2	75%
	Grade 3 or 4	Discuss with consultant
Diarrhoea	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%
Stomatitis	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infusion related reactions
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility
Cardiotoxicity
Peripheral neuropathy
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of fluorouracil treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of fluorouracil and is usually reversible on discontinuing the infusion. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the fluorouracil should be permanently discontinued.

- **Frequently occurring side effects**

Diarrhoea

Stomatitis and mucositis
Palmar-plantar erythema
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Arthralgia and myalgia

- **Other side effects**

Alopecia
Fluid retention Deranged liver function
Phlebitis
Skin toxicity Nail changes

Significant drug interactions – for full details consult product literature/ reference texts

Oxaliplatin:

Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.

Fluorouracil:

Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Docetaxel:

CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Avoid use in patients with known DPD deficiency.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

Driving and using machines

Alcohol used in Docetaxel may impair ability to drive or use machines. Patients should be advised not to drive or use machinery 1-2 hrs post infusion.

References

- Summary of Product Characteristics Durvalumab via https://www.medicines.org.uk
- Summary of Product Characteristics Oxaliplatin via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil via www.medicines.org.uk
- Summary of Product Characteristics Docetaxel via www.medicines.org.uk
- Janjigian YY, et al. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. N Engl J Med. 2025; doi:10.1056/NEJMoa250370

THIS PROTOCOL HAS BEEN DIRECTED BY DR MITCHELL, DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: May 2026
Review: May 2026
VERSION: 1