

# Nivolumab FOLFOX (nivolumab, oxaliplatin, folinic acid and fluorouracil)

## Indication

First line treatment for advanced gastric, gastro-oesophageal junction and oesophageal adenocarcinoma

## Regimen details

### Combination chemo/immunotherapy:

Day	Drug	Dose	Route
1	Nivolumab	600mg Or 240mg	Subcutaneous or Infusion
1	Calcium folinate	350mg	IV infusion
1	Oxaliplatin	85mg/m <sup>2</sup>	IV infusion
1	Fluorouracil	400mg/m <sup>2</sup>	IV bolus
1-2 (46 hours)	Fluorouracil	2400mg/m <sup>2</sup>	IV infusion over 46 hours

Every 14 days for 12 cycles

### Followed by:

Nivolumab 1200mg subcutaneous

Or

Nivolumab 480mg infusion

Every 28 days for up to 2 years

## Cycle frequency

See above

## Number of cycles

See above

## Administration

Nivolumab infusion is given in 50ml 0.9% sodium chloride over 30 minutes

Patients should be monitored during the infusion for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Nivolumab injection is given over 3-5 minutes into the subcutaneous tissue of the abdomen or thigh. Alternate injection sites for successive injections.

If the administration of nivolumab is interrupted, it can be resumed at the same site, or at an alternate site. Monitor patients during and after administration for signs and symptoms of adverse reactions. During the treatment course with nivolumab solution for injection, other medicinal products for subcutaneous administration should preferably be injected at different sites.

Oxaliplatin is administered in 250mL glucose 5% over 2 hours. This is infused **concurrently** with calcium folinate 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. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of 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 re- started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.

Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy should be initiated.

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 well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Fluorouracil is administered as an IV bolus injection over 5 minutes.

Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device over 46 hours or as a continuous peripheral IV infusion over 46 hours in 2 x 1000mL sodium chloride 0.9%.

### Pre-medication

Antiemetics as per local policy.

Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:

- 30 minutes prior to Oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to Oxaliplatin: Chlorphenamine 10mg IV and Ranitidine 50 mg IV

### Emetogenicity

This regimen has a moderate-high emetogenic potential

### Additional supportive medication

Mouthwashes as per local policy. Loperamide if required.

### Extravasation

Oxaliplatin is an exfoliant (Group 4).

Fluorouracil is an inflammatant (Group 2)

Nivolumab is neutral (Group 1)

### Investigations – pre first cycle

Standard pre-SACT tests

DPYD test

### Investigations - pre subsequent cycles

FBC, U&Es, LFT (including AST), calculated creatinine clearance, calcium, magnesium, random glucose, CEA

### 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	$\geq 1.5 \times 10^9/L$ (discuss with consultant $\geq 1.0$ - $<1.5$ )

Platelets	≥ 75 x 10 <sup>9</sup> /L
Bilirubin	< 1.5 x ULN
AST/ALT	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min (see dose modifications below)

- **Immunotherapy toxicity**

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>

### Dose modifications

**Do not amend the dose of nivolumab**

- **DPYD variants**

All patients due to receive fluoro-pyrimidine based therapy should have a DPD test prior to starting treatment. 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).

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. Patients with variants should be considered for a dose modification following national advice for recommended dose adjustments.

[https://www.uksactboard.org/files/ugd/638ee8\\_4d24d37a598c485d9ef4d1ba90abccd5.pdf](https://www.uksactboard.org/files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf)

Where a patient has had significant toxicities but the DPD test has shown none of the variants to be present, a further test can be conducted to test the presence of rarer variants.

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.0 x 10<sup>9</sup>/L and/or platelets < 75 x 10<sup>9</sup>/L.

Neutrophils	Platelets	Oxaliplatin dose	5 Fluorouracil dose
≥1.0 and	≥75	100%	100%
0.5-0.9 or	50-74	65mg/m <sup>2</sup>	100%
<0.5 and/or	25-49	65mg/m <sup>2</sup>	100%
<0.5 and/or	<25	55mg/m <sup>2</sup>	100%

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

- **Renal impairment**

CrCl (mL/min)	Oxaliplatin dose	Fluorouracil dose
≥ 50	100%	100%
30-49	100%	100%
10-29	65mg/m <sup>2</sup>	100%
< 10	Omit	Consider dose reduction

- **Hepatic impairment**

Bilirubin (x ULN)		AST/ALT (x	Oxaliplatin dose	Fluorouracil dose
≤ 1.5	and	≤ 1.5	100%	100%
1.5 - 3	and	≤ 3	100%	Consider dose reduction*

3 – 5	or	3 – 5	50%	Consider dose reduction*
> 5	or	> 5	omit	Contraindicated

\*consultant decision

- **Other toxicities**

For all toxicities, delay treatment until resolved to  $\leq$  Grade 1. Then reduce doses as per the following table:

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

\* Patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid (sometimes fatal) deterioration can occur.

**Neurological toxicity:**

Dose related peripheral neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m<sup>2</sup>. It can occur once oxaliplatin is completed.

If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	Oxaliplatin
1 (any duration) or grade 2 longer than 7 days	100%
2 paraesthesia persisting until next cycle	75mg/m <sup>2</sup>
3 paraesthesia lasting longer than 7 days	75mg/m <sup>2</sup>
3 paraesthesia persisting until next cycle	Discontinue permanently
4 of any duration	Discontinue permanently

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

- **Serious side effects**

Immunotherapy toxicity  
 Myelosuppression  
 Infertility  
 Allergic reactions  
 Neurotoxicity  
 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**

Nausea and vomiting  
 Diarrhoea  
 Stomatitis and mucositis  
 Palmar-plantar erythema  
 Alopecia

Fatigue  
Dyspnoea

- **Other side effects**

Transient cerebellar syndrome  
Confusion

**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.

**Corticosteroids:** use of systemic corticosteroids at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

**Additional comments**

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/m<sup>2</sup>. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

**Fertility/Contraception**

Patients should agree to use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breast feeding should be discontinued during treatment. Oxaliplatin may have an anti-fertility effect.

**References**

- Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma Technology appraisal guidance Reference number:TA857
- Published: 11 January 2023
- Summary of Product Characteristics (Oxaliplatin) accessed 17 April 2025 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Summary of Product Characteristics (Fluorouracil) accessed 17 April 2025 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Personalised Medicine Approach for Fluoro-pyrimidine-based Therapies. UK Chemotherapy Board V2 September 2024 accessed 17 April 2025 via [https://www.uksactboard.org/files/ugd/638ee8\\_4d24d37a598c485d9ef4d1ba90abccd5.pdf](https://www.uksactboard.org/files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf)

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

Lancashire & South Cumbria Cancer Alliance  
Systemic Anticancer Treatment Protocol

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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