NIVOLUMAB (Opdivo) OXALIPLATIN Modified de Gramont

INDICATION (ICD10) C15, C16

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

1. Nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated advanced unresectable or metastatic HER-2 negative adenocarcinomas of the stomach, gastro-oesophageal junction or oesophagus which express PD-L1 with a combined positive score of 5 or more, who have not received any previous immunotherapy except as part of adjuvant therapy, completed at least 6 months ago without progression. PS 0 or 1. (TA

2. Nivolumab in combination with platinum and fluoropyrimidine-based chemotherapy for previously untreated unresectable advanced unresectable or recurrent or metastatic squamous cell carcinoma of the oesophagus with a tumour cell PD-L1 expression of =>1% and a PD-L1 combined positive score of <10, not previously treated with PD-1 or PD-L1 or PD-L2 or CD137 or OX40 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) treatments.PS 0 or 1. (TA

REGIMEN

Day 1 NIVOLUMAB 240mg** in 100ml sodium chloride IV infusion over 30 minutes
OXALIPLATIN 85mg/m^2 in 250ml* glucose 5% IV infusion over 2 hours
CALCIUM LEVOFOLINATE 175mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin via a Y site placed immediately before the injection site
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

*oxaliplatin doses 225mg to 395mg in 500ml glucose 5%
**if oxaliplatin and fluorouracil are discontinued nivolumab 480mg every 28 days must be used

NB Calcium levofolinate is not the same as calcium folinate (calcium leucovorin).
Calcium levofolinate is a single isomer of folinic acid and the dose is generally half that of calcium folinate. If calcium levofolinate is not available calcium folinate (leucovorin) may be used instead.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14** days
until progression for up to maximum 2 calendar years from start date (Irrespective of any breaks in treatment).

ANTI-EMETICS

Moderately emetogenic day 1
Low emetogenic risk day 2

CONCURRENT MEDICATION REQUIRED

Fluorouracil	Mouth and bowel support eg Loperamide, benzydamine mouthwash
Oxaliplatin	Flush with glucose 5% after infusion

EXTRAVASATION AND TYPE OF LINE / FILTERS

Fluorouracil – inflammitant
Nivolumab - neutral
Oxaliplatin - exfoliant

Use low protein binding 0.2 to 5micron in-line or add-on filter for nivolumab.
Central line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs and creatinine every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
DPYD test
Baseline weight and every cycle
ECG (possible ECHO) required if patient has preexisting cardiac disease

MAIN TOXICITES AND ADVERSE REACTIONS

Fluorouracil	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. Special attention is advisable in treating patients with a history of heart disease, arrhythmias or angina pectoris or those who develop chest pain during treatment with fluorouracil. Stomatitis
Nivolumab	Immune related toxicities - pneumonitis, colitis or hepatitis etc
Oxaliplatin	Peripheral sensory neuropathy and laryngeal spasm – avoid cold drinks and touching cold items

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Fluorouracil	Cimetidine slightly increases exposure to fluorouracil Metronidazole increased toxicity Phenytoin concentration increased Warfarin

DOSE MODIFICATIONS

Haematological

If neutrophils <1.5x10^9/L or platelets <100x10^9/L delay 1 week, only treat when neutrophils and platelets are above these limits.
If grade 4 neutropenia consider giving 50% oxaliplatin and fluorouracil in palliative disease.
If >1 delay or 1 delay ≥2 weeks reduce all the oxaliplatin and fluorouracil doses to give 80% for future cycles. Dose reductions may be made at the Clinician's discretion.

Non-haematological

Nivolumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline

Oxaliplatin

If patients develop acute laryngopharyngeal dysaesthesia infuse the next cycle over 4 hours.
If symptoms persist give 80% dose.
If persistent sensory symptoms occur, withdraw treatment

Hepatic impairment

Fluorouracil

Significantly impaired hepatic function eg bilirubin >50micromol/L may be a sign of disease progression and require cessation of, or change in, treatment. Always discuss deteriorating liver function with consultant.

Bilirubin >85micromol/L	not recommended

Nivolumab

Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions. Nivolumab should be administered with caution in patients with moderate or severe hepatic impairment ie bilirubin >1.5xULN and any AST.

Renal impairment

Fluourouracil

CrCl >30ml/min	give 100% dose
CrCl <30ml/min	consider dose reduction

Nivolumab

Data from patients with severe renal impairment (CrCl <30ml/min) are too limited to draw conclusions.

Oxaliplatin

CrCl >30ml/min	give 100% dose
CrCl <30ml/min	Dose reduce (consider 50% of original dose)

REFERENCES

1. Blueteq