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/) (NIV21) (NIV22)

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. (TA857)
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. (TA865)

REGIMEN IV then SC

Cycles 1 to 12

Day 1	NIVOLUMAB	240mg** in 100ml sodium chloride IV infusion over 30 minutes
	OXALIPLATIN	85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
	CALCIUM FOLINATE	350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
	FLUOROURACIL	400mg/m^2 IV bolus
	FLUOROURACIL	2400mg/m^2 continuous IV infusion over 46 hours

**if oxaliplatin and fluorouracil are discontinued nivolumab 480mg every 28 days must be used

Cycles 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49 and 51

Day 1	NIVOLUMAB	1200mg subcutaneous over 3 to 5 minutes

REGIMEN IV

Cycles 1 to 11

Day 1	NIVOLUMAB	240mg** in 100ml sodium chloride IV infusion over 30 minutes
	OXALIPLATIN	85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
	CALCIUM FOLINATE	350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
	FLUOROURACIL	400mg/m^2 IV bolus
	FLUOROURACIL	2400mg/m^2 continuous IV infusion over 46 hours

Cycle 12

Day 1	NIVOLUMAB	480mg in 100ml sodium chloride IV infusion over 30 minutes
	OXALIPLATIN	85mg/m^2 in #ml glucose 5% IV infusion over 2 hours
	CALCIUM FOLINATE	350mg in glucose 5% IV infusion over 2 hours concurrently with oxaliplatin
	FLUOROURACIL	400mg/m^2 IV bolus
	FLUOROURACIL	2400mg/m^2 continuous IV infusion over 46 hours

Cycles 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52

Day 1	NIVOLUMAB	480mg in 100ml sodium chloride IV infusion over 30 minutes

**if oxaliplatin and fluorouracil are discontinued nivolumab 480mg every 28 days must be used

diluent and diluent volume for dose prescribed as per national standardised product specification

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 14 days for 12 cycles.
Nivolumab monotherapy every 28 days from cycle 12 ie even number cycles only
Treatment until progression for up to a maximum 2 calendar years from start date the cycle 1 combination (irrespective of any breaks in treatment).

ANTI-EMETICS

Moderately emetogenic day 1 cycles 1 to 12
Low emetogenic risk day 2 cycles 1 to 12
Minimal emetogenic risk day 1 cycles 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 and 52

CONCURRENT MEDICATION REQUIRED

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

ADMINISTRATION

Nivolumab	SC administer in the abdomen or thigh over 3 to 5 minutes. Alternate injection sites.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Fluorouracil – inflammitant
Nivolumab IV - 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 (dihydropyrimidine dehydrogenase) test
Baseline weight and every cycle

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.	
If hepatic function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected in mild and moderate (without renal impairment).	
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.

Oxaliplatin
No dose adjustment is needed.

Renal impairment
Fluourouracil

If renal function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected.

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. CDF list