NIVOLUMAB (Opdivo) OXALIPLATIN CAPECITABINE (CapOx or OX versions)

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 8

Day 1	NIVOLUMAB	360mg** in 100ml sodium chloride IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in #ml glucose 5% IV infusion over 2 hours
Days 1 to 14	CAPECITABINE	1000mg/m^2 twice daily (2000mg/m^2/day) oral followed by a 7 day rest (CapOx)

or

Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously (OX)

Cycle 9 up to 2 calendar years from treatment start

Day 1	NIVOLUMAB	1200mg subcutaneous over 3 to 5 minutes

REGIMEN IV

Cycles 1 to 8

Day 1	NIVOLUMAB	360mg** in 100ml sodium chloride IV infusion over 30 minutes
	OXALIPLATIN	130mg/m^2 in #ml glucose 5% IV infusion over 2 hours
Days 1 to 14	CAPECITABINE	1000mg/m^2 twice daily (2000mg/m^2/day) oral followed by a 7 day rest (CapOx)

or

Days 1 to 21	CAPECITABINE	625mg/m^2 twice daily (1250mg/m^2/day) oral continuously (OX)

Cycle 9 every 28 days up to 2 calendar years from treatment start

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

**if oxaliplatin and capecitabine are discontinued then nivolumab SC 1200mg or nivolumab IV 480mg every 28 days must be used instead.

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Combination every 21 days for 8 cycles

Nivolumab monotherapy every 28 days from cycle 9

Treatment until progression for up to a maximum of 2 calendar years from the start date of the cycle 1 combination (irrespective of any breaks in treatment).

ADMINISTRATION

Tablets should be taken 12 hours apart.
Swallowed with water within 30 minutes after a meal, or dissolve in 200ml luke warm water, stir thoroughly (squash may be added if unpalatable).

ANTI-EMETICS

Moderately emetogenic day 1 cycles 1 to 8
Low emetogenic risk days 2 to 14 cycles 1 to 8
Minimal emetogenic risk every 28 days cycle 9 onwards

CONCURRENT MEDICATION REQUIRED

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

EXTRAVASATION AND TYPE OF LINE / FILTERS

Nivolumab IV - neutral
Oxaliplatin - exfoliant

Use low protein binding 0.2 to 5micron in-line or add-on filter for nivolumab.
Central or peripheral 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
Baseline weight and every cycle
DPYD (dihydropyrimidine dehydrogenase) test

MAIN TOXICITES AND ADVERSE REACTIONS

Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine Cardiotoxicity – monitor cardiac function. To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. 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)

Capecitabine	Brivudine and analogues should be avoided Warfarin and caution with all oral anticoagulants Phenytoin Allopurinol

DOSE MODIFICATIONS
Non-haematological
Capecitabine
Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome.
Toxicity can be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction).
Once the dose has been reduced it should not be increased at a later time.
When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

Toxicity Grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 1st appearance	Discontinue permanently OR if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

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

Capecitabine

Bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt Capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

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

Capecitabine

CrCl (ml/min) >50	give 100% dose
CrCl (ml/min) 30-50	give 75% dose
CrCl (ml/min) <30	contraindicated

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