NIVOLUMAB (Opdivo) PEMETREXED CARBOPLATIN

INDICATION (ICD10) C34
Check the most recent Bluteq eligibility criteria before prescribing. Bluteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

1. Nivolumab plus chemotherapy for the neoadjuvant treatment of adults with previously untreated UICC/AJCC 8th edition stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer (stage M0 without an EGFR 19 or 21 mutation or ALK gene fusion) tumours at least 4 cm or node positive and who are candidates for potentially curative surgery within 6 weeks of completing the 3rd cycle. Check Bluteq criteria carefully for eligibility for future treatments. PS 0 or 1.

REGIMEN
Carboplatin to start 30 minutes after completing pemetrexed
Day 1 NIVOLUMAB 360mg IV infusion in 100ml sodium chloride IV infusion over 30 minutes
Pre-medication: Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy)
Pemetrexed 500mg/m² in 100ml sodium chloride 0.9% or glucose 5% depending on pemetrexed brand used IV infusion over 10 minutes
Carboplatin AUC 5 in 500ml glucose 5% IV infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

CYCLE FREQUENCY AND NUMBER OF CYCLES
Every 21 days for maximum 3 cycles (must be formally reviewed before end of 2nd cycle)

ANTI-EMETICS
Moderate emetic risk day 1

CONCURRENT MEDICATION REQUIRED

<table>
<thead>
<tr>
<th>Carboplatin</th>
<th>Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus H₂ antagonist Carboplatin should be given at a slower rate e.g. 2–4 hours.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>Ensure premedication taken Dexamethasone 4mg bd for 3 days (starting the day before chemotherapy) Folic acid 400mcg/day orally starting 1 to 3 weeks before chemotherapy continuing until 21 days after the last dose of pemetrexed. Hydroxycobalamin 1000mcg IM every 9 weeks starting 1 to 3 weeks before chemotherapy (give with every 3rd cycle of chemotherapy)</td>
</tr>
</tbody>
</table>

EXTRAVASATION AND TYPE OF LINE / FILTERS
Carboplatin – irritant Nivolumab – neutral Pemetrexed - inflammatory

Nivolumab use low protein binding 0.2 to 1.2micron in-line or add-on filter. Peripheral line
INVESTIGATIONS
Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils $\geq 1.5$ x $10^9/L$
Platelets $\geq 100$ x $10^9/L$
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant’s discretion. Patients with hydronephrosis or serum creatinine $\geq 100$ micromol/L need a serum creatinine checked every cycle.
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
</tr>
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<tbody>
<tr>
<td>Carboplatin</td>
<td>Ototoxicity - monitor</td>
</tr>
<tr>
<td></td>
<td>Neurotoxicity – monitor.</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Immune related toxicities - pneumonia, colitis or hepatitis etc</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Skin reactions</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
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</table>

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

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<th>Drug</th>
<th>Interaction</th>
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<tr>
<td>Carboplatin</td>
<td>Aminoglycosides increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests as required. Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Skin reactions</td>
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<tr>
<td></td>
<td>Pneumonitis</td>
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</tbody>
</table>

DOSE MODIFICATIONS
Haematological

Pemetrexed
Delay treatment until resolution then treat with appropriate dose modification.
Nadir neutrophils $<0.5$ and nadir platelets $>50$ 75% of previous dose
Nadir platelets $\leq 50$ regardless of nadir neutrophils 50% of previous dose
Treatment with pemetrexed should be discontinued if a patient experiences any haematologic or non-haematologic Grade 3 or 4 toxicity after 2 dose reductions

Non-haematological
Nivolumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline
Pemetrexed

<table>
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<th>Any Grade 3 or 4 non-haematological toxicities except mucositis</th>
<th>Give 75% of previous dose</th>
</tr>
</thead>
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<tr>
<td>Any diarrhoea requiring hospitalisation (irrespective of grade) or grade 3 or 4 diarrhoea</td>
<td>Give 75% of previous dose</td>
</tr>
<tr>
<td>Grade 3 or 4 mucositis</td>
<td>Give 50% of previous dose</td>
</tr>
<tr>
<td>Neurotoxicity grade 3 or 4</td>
<td>Discontinue therapy</td>
</tr>
<tr>
<td>If a patient experiences any haematological or non-haematological grade 3 or 4 toxicity after 2 dose reductions or immediately if grade 3 or 4 neurotoxicity is observed</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

**Hepatic impairment**

**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 i.e. bilirubin >1.5xULN and any AST.

**Pemetrexed**

Total bilirubin should be ≤1.5xULN.

Alk phos, AST and ALT ≤3xULN. (Alk phos, AST, and ALT ≤5x normal is acceptable if liver has tumour involvement). Clinical decision

**Renal impairment**

**Carboplatin**

| GFR/ calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment | contraindicated |

**Nivolumab**

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

**Pemetrexed**

| CrCl ≤45ml/min | Not recommended |

**REFERENCES**