PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

# Neoadjuvant Platinum/Paclitaxel /Nivolumab NSCLC

**PROTOCOL REF: MPHANPPN**

**Version No: 1.1**

## Approved for use in:

Nivolumab in combination with platinum- based chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer (NSCLC) who satisfy the following criteria:

- Tumours ≥ 4 cm or node positive (stage IIA or IIB or IIIA or N2 only IIIB tumour according to the UICC/AJCC TNM 8th edition).
- NEGATIVE for EGFR 19 or 21 mutation or an ALK gene fusion (NOT a requirement for squamous histology).
- Potentially curative resection to proceed within 6 weeks of completing the final cycle of neoadjuvant nivolumab plus chemotherapy.
- ECOG performance status (PS) of 0 or 1.
- <u>Following neoadjuvant SACT and successful resection:</u>
    - Adjuvant chemotherapy is PERMITTED if indicated.
    - Adjuvant immunotherapy is NOT PERMITTED.
    - Adjuvant radiotherapy or chemoradiotherapy (CRT) is PERMITTED if indicated.
- <u>During neoadjuvant SACT:</u>
    - If disease progression occurs then further immunotherapy is NOT funded IN ANY INDICATION.

- If disease progression does NOT occur and surgical resection does NOT proceed then further immunotherapy is ONLY PERMITTED following a disease response of at least 6 months (duration from last Nivolumab dose to progressive disease). UNLESS stage III disease and treated with **concurrent chemoradiotherapy** then potentially eligible for maintenance durvalumab.

**Blueteq Registration Required**

**Exclusions**

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, active hepatitis B or C infection
- Active infection requiring systemic treatment
- Less than 4 weeks from major surgery
- History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)
- Patient with active CNS disease or carcinomatosis meningitis
- Pregnancy or breast feeding

## Dosage:

**Cycles 1 to 3**

| Drug | Dosage | Route | Frequency and duration |
|---|---|---|---|
| Nivolumab | 360mg | IV Infusion | 3 weekly for 3 cycles |
| Paclitaxel | 175mg/m² | | |
| Carboplatin | AUC 5 | | |

**Carboplatin**

Calvert formula for Carboplatin dosage:

*Carboplatin dose in mg = AUC x (creatinine clearance + 25)*

Meditech calculates creatinine clearance using the Wright formula, the Carboplatin Dose Calculator application for calculating creatinine is available on the Remote Citrix Web Portal. Please refer to 'Carboplatin Dosing Calculator SOP' for full details. If estimated GFR is used the **Wright formula** must be used for creatinine clearance.

Creatinine clearance should be **capped at 125mL/min** for carboplatin

Avoid the use of Cockcroft and Gault formulae as it is less accurate.

## Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of Nivolumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Flu like symptoms are common, particularly during cycle 1
- Monitor for signs of infection / sepsis as this regimen is associated with neutropenia

## Emetogenic Risk:

Highly emetogenic

## Extravasation risk:

Refer to the CCC policy for the '**Prevention and Management of Extravasation Injuries**'**.**

**Carboplatin-** IRRITANT

**Paclitaxel-** VESICANT

**Nivolumab-** NEUTRAL

## Supportive Treatments:

Dexamethasone tablets 4mg orally twice daily for three days

Metoclopramide tablets 10mg oral, up to 3 times a day or as required for a maximum of 5 consecutive days.

Ondansetron 8mg twice a day when required for nausea and vomiting.

Aprepitant capsules 125mg oral 1 hour before chemotherapy then 80mg as a single dose on day 2 and 3 of treatment cycle (2nd line anti-emetic).

Filgrastim to be supplied as primary (≥ 1 risk factor*) or secondary prophylaxis – subcutaneous (SC) injection daily for 7 days starting on day 5, dose as follows:

- Weight < 70kg- Filgrastim 300 micrograms daily SC.
- Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.

*Risk factors for neutropenic sepsis:

- Prior chemotherapy or radiotherapy
- Persistent neutropenia
- Bone marrow involvement by tumour
- Recent surgery and/or open wounds
- Liver dysfunction (bilirubin > 43 micromol/dl)
- Renal dysfunction (creatinine clearance <50ml/min)
- Age >65 years receiving full chemotherapy dose intensity

## Dosing in renal and hepatic impairment:

| | | |
|---|---|---|
| Renal dosing | Nivolumab (prior to start of treatment ONLY/Baseline) | GFR ≥ 30ml/min proceed with treatment<br>GFR < 30ml/min- limited data, use with caution. |
| | Paclitaxel | All grades including patients on haemodialysis - no dose adjustment required. |

<table>
<tr><td></td><td>Carboplatin</td><td>Carboplatin is eliminated primarily in the urine and is nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.<br>Ahead of each cycle of treatment calculate GFR using the Wright formula (refer to ‘Administration’ Section) prior to treatment with carboplatin. Please refer to ‘Carboplatin Dosing Calculator SOP’ for full details.<br>If CrCl ≤ 20ml/min<br>Discuss with clinical team prior to administration</td></tr>
</table>

<table>
<tr><td rowspan="3">Hepatic dosing</td><td>Nivolumab<br>(prior to start of treatment ONLY/Baseline)</td><td>Limited data- administered with caution in patients with:<br>Moderate (total bilirubin > 1.5 -3 × ULN and any AST*)<br>or<br>Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment.<br>* Within normal limits or high</td></tr>
<tr><td>Paclitaxel</td><td>
<table>
<tr><th>Bilirubin</th><th></th><th>ALT and/or AST</th><th>Dose</th></tr>
<tr><td>≤ 1.25x ULN</td><td rowspan="3">AND</td><td rowspan="3">< 10 x ULN</td><td>175mg/m$^2$</td></tr>
<tr><td>1.26 to 2xULN</td><td>135mg/m$^2$</td></tr>
<tr><td>2.01 to 5xULN</td><td>90mg/m$^2$</td></tr>
<tr><td>> 5xULN</td><td>OR</td><td>≥10 x ULN</td><td>NOT TO BE GIVEN</td></tr>
</table>
</td></tr>
<tr><td>Carboplatin</td><td>No dose reductions necessary</td></tr>
</table>

## Interactions:

For more detailed interactions please refer to the SmPC for each agent.

| Nivolumab |
| --- |
| The use of systemic corticosteroids and other immunosuppressants before starting nivolumab should be avoided because of their potential interference with the pharmacodynamic activity. But they can be used after starting nivolumab to treat immune-related adverse reactions. Studies have shown show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab. |
| Paclitaxel |
| Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.<br>Studies in Kaposi's Sarcoma patients, who were taking multiple concomitant medicinal product, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy. |
| |

## Carboplatin

Concomitant use contraindicated

Yellow fever vaccine: risk of generalized disease mortality.

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin).

Concomitant use to take into consideration

- Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance.
- Loop diuretics (e.g. furosemide, indapamide): The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

## Administration:

**Cycles 1 to 3**

| Day | Drug | Dose | Route | Diluent and Rate |
|---|---|---|---|---|
| 1 | Nivolumab | 360mg | IV infusion | 100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron to 1.2 micron filter |
| 1 | Dexamethasone | 16.5mg | IV bolus | 30 minutes before chemotherapy |
| 1 | Ondansetron | 16mg | Oral | 30 minutes before chemotherapy |
| 1 | Famotidine | 20mg | Oral | At least 60 minutes before chemotherapy |
| 1 | Chlorphenamine | 10mg | IV bolus | 30 minutes before chemotherapy |
| 1 | Paclitaxel | 175mg/m² | IV Infusion | 500mL sodium chloride 0.9% over 3 hours using a non-PVC giving set with a 0.22 micron filter |
| 1 | Carboplatin | AUC 5 | IV Infusion | 500mL glucose 5% over 30 to 60 minutes |

**Every 3 weeks for 3 cycles**

NOTE- Paclitaxel:

- Must be administered using a non-PVC giving set with a 0.22 micron filter prior to carboplatin
- In solution may show haziness which is attributed to the specific paclitaxel formulation.

- Avoid excessive shaking, agitation, or vibration of paclitaxel may induce precipitation.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). Please refer to the CCC Hypersensitivity; Management Prevention Policy.

## Main Toxicities:

| | |
|---|---|
| **Nivolumab in combination with paclitaxel and carboplatin** | **The most common adverse reactions:**<br>• Any grade- nausea, anaemia, constipation, decreased appetite and decreased neutrophil count.<br>• Grade 3/4- neutropenia, decreased neutrophil count, anaemia, decreased appetite, Nausea. |

| Nivolumab<br>For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management. | |
|---|---|
| Immune-Mediated Pneumonitis<br><br>Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%). | Refer to Immuno-Oncology toxicity specific guidance for adverse event management |
| Immune-Mediated Colitis<br><br>Colitis occurred in 1% of patients (including G3 in 0.5%). | Refer to Immuno-Oncology toxicity specific guidance for adverse event management |

| | |
|---|---|
| Other Immune-Mediated Toxicities:<br>Hypophysitis<br>Nephritis<br>Hyperthyroidism or Hypothyroidism<br><br>Less frequently:<br>Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia | Monitor LFTs, biochemistry, cortisol and TFTs regularly<br><br>Refer to Immuno-Oncology toxicity specific guidance for adverse event management |
| Other non-immune adverse events:<br>Fatigue, anaemia<br>Cough, dyspnoea<br>Nausea, decreased appetite<br>Pruritis, rash<br>Constipation, diarrhoea<br>Arthralgia | ***See specific guidance below for arthralgia/myalgia**<br><br>Refer to Immuno-Oncology toxicity specific guidance for adverse event management |
| Laboratory abnormalities:<br>Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia | Refer to Immuno-Oncology toxicity specific guidance for adverse event management |
| Paclitaxel | |
| Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia. | |
| Carboplatin | |
| Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), ototoxicity, arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia. | |

## Investigations and treatment plan

**If suspicion of endocrinopathies:** request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Ongoing |
|---|---|---|---|---|---|
| Informed Consent | x | | | | |
| Clinical Assessment/Review | x | | x | x | Every cycle and as clinically indicated |
| SACT Assessment (to include PS and toxicities) | x | x | x | x | Every cycle* |
| | **If SACT is deferred patient must be booked in for clinical review prior to next cycle.** | | | | |
| OTR | x | x | x | x | Every cycle prior to nivolumab treatment |
| Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (AST, ALT and bilirubin), TFTs, cortisol, blood glucose, LDH, CRP | x | x | x | x | Every cycle |
| Lipid profile (cholesterol) | x | | | | At baseline then if clinically indicated |
| Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR | x | | | | At baseline then if clinically indicated |
| Full set of observations (*BP, heart rate, temperature, respiratory rate and $O_2$ sats*) | x | x | x | x | Every cycle |
| Creatinine Clearance (Cockcroft and Gault) | x | x | x | x | Every cycle |
| Radiological staging (CT chest and abdomen or PET-CT and MRI Brain as appropriate) **Guidance for clinical teams ONLY** | x | | | | PET-CT +/- MRI Brain at baseline then radiological restaging (CT or PET-CT) after cycle 2 or 3. |
| Trop-T, CK, pro-BNP | x | | | | At baseline and thereafter as clinically indicated Refer to 'Pre-assessment Baseline Cardiac Pathway' |
| ECG | x | | | | |
| Weight recorded | x | x | x | x | Every cycle |
| Height recorded | x | | | | |

***Refer to 'Dose Modifications and Toxicity Management' section**

## Dose Modifications and Toxicity Management:

- **If SACT is deferred patient must be booked in for clinical review prior to next cycle.**
- Dose modifications due to toxicity are ONLY permitted on chemotherapy agents (paclitaxel, carboplatin).
- Only dosing delay or discontinuation due to toxicity are permitted for nivolumab.
- Guidelines for permanent discontinuation or withholding of nivolumab doses are contained in 'Treatment Threshold' section below.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.
- If either the Nivolumab or the chemotherapy are discontinued then the other agent(s) can be continued.

| Dose Level | Carboplatin | Paclitaxel |
|---|---|---|
| Starting dose | AUC 5 | 175mg/m$^2$ |
| First dose reduction | AUC 4 | 150mg/m$^2$ |
| Second dose reduction | AUC 3 | 100mg/m$^2$ |
| 3$^{rd}$ dose reductions NOT permitted- discontinue chemotherapy agent. | | |

# Treatment Threshold

**Nivolumab, Paclitaxel, Carboplatin**

Administer treatment on day 1 if:

| SACT | Platelets | Neutrophils | Serum Creatinine | Bil | AST/ ALT | ALP | TSH and Free T4 |
|---|---|---|---|---|---|---|---|
| Nivolumab | ≥ 100 x $10^9$/L **(Must be within normal range prior to cycle 1*)** | ≥ 1.0 x $10^9$/L | ≤1.5 x ULN or baseline | <3 x ULN | <5 x ULN | <5 x ULN | Within range or no change from base line |
| Paclitaxel and carboplatin | | | **Refer to 'Dosing in renal and hepatic impairment' section for recommended dose modifications for carboplatin and paclitaxel based on individual renal and hepatic function** | | | | |

ULN = upper limit of normal
*****If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction

## Nivolumab

Dose reduction NOT permitted. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

***Arthralgia/Myalgia:**
Consider taxane-induced pain. Arthralgia or myalgia affects 60% of patients treated with paclitaxel. Typically occurs 1-3 days after treatment and persists for 2-8 days. Should be managed with analgesia including escalation to opioid analgesia if severe. Dosing can be continued following the guidance below. In subsequent cycles, patients should be encouraged to take regular analgesia starting 24hrs pre-dose.

| Toxicity Grade | Action |
|---|---|
| **Grade 1**<br>Mild | Continue treatment increase monitoring and provide symptomatic treatment. |
| **Grade 2**<br>Moderate | Withhold treatment until resolved to ≤ grade 1.<br><br>Refer to Immuno-Oncology toxicity specific guidance for adverse event management. |
| **Grade 3 and Grade 4**<br>Severe | Withhold treatment.<br><br>Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion.<br><br>Refer to Immuno-Oncology toxicity specific guidance for adverse event management. |

**Haematological Toxicity:**

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment, treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

| Toxicity | Grade | Carboplatin | Paclitaxel |
|---|---|---|---|
| Neutropenia | **Grade 4**<br>< 0.5 x $10^9$/L | Reduce one dose level and consider prophylactic G-CSF in subsequent cycles | Reduce one dose level and consider prophylactic G-CSF in subsequent cycles |
| Febrile Neutropenia | **Grade ≥ 3**<br>Neutrophils < 1.0 x $10^9$/L with a single temperature of >38.3ºC or a sustained temperature of ≥ 38ºC for more than one hour | Reduce one dose level | Reduce one dose level |
| Thrombocytopenia | **Grade 3**<br>25.0 to < 50.0 x $10^9$/L | Reduce one dose level | Reduce one dose level |
| | **Grade 4**<br>< 25.0 x $10^9$/L | Reduce one dose level | Reduce one dose level |
| Anaemia | **Grade 2**<br>< 100 - 80 g/L | Reduce one dose level | Reduce one dose level |
| | **Grade 3**<br>< 80 g/L | Reduce one dose level | Reduce one dose level |
| | **Grade 4**<br>(Life threatening consequences) | Hold Drug | Hold drug |
| Allergic reaction or IRR | **Grade ≥ 3**<br>Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated | Only the drug causing the hypersensitivity reaction should be discontinued. | |
| Neuropathy | **Grade 2** | No change | Reduce one dose level |

| | | | |
|---|---|---|---|
| | **Grade ≥ 3** | Discontinue | Discontinue |
| Creatinine clearance calculated using (Cockcroft and Gault) | | Discontinue if creatinine clearance < 20 mL/min | No change |
| Arthralgia/Myalgia | **Grade 2** Moderate pain; limiting instrumental ADL | No change | No change |
| | **Grade 3** Severe pain; limiting self care ADL | No change | Reduce one dose level |

## References:


Carboplatin 10 mg/ml concentrate for solution for infusion SmPC, Accord Healthcare Ltd, Middlesex. Available from www.medicines.org.uk/emc/medicine. Last updated 31st August 2018.

Forde, P.M., Spicer, J., Lu, S., Provencio, M., Mitsudomi, T., Awad, M.M., Felip, E., Broderick, S.R., Brahmer, J.R., Swanson, S.J. and Kerr, K., 2022. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *New England Journal of Medicine*, 386(21), pp.1973-1985.

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.

NICE Clinical Guideline (CG151) Neutropenic sepsis: prevention and management in people with cancer. Published 19th September 2012.

NICE TA (TA876) Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer. Published: 22 March 2023

OPDIVO 10 mg/mL concentrate for solution for infusion, Summary of Product Characteristics, Bristol Myers Squibb Pharmaceuticals limited. Available from www.medicines.org.uk/emc/medicine. Last updated 4th November 2022.

Paclitaxel 6 mg/ml concentrate for solution for infusion SmPC Hospira UK Ltd, Warwickshire Available from www.medicines.org.uk/emc/medicine. Last updated 27th April 2020.

## Circulation/Dissemination

| | |
|---|---|
| Date added into Q-Pulse<br><br>Date document posted on the Intranet | |

## Version History

| Date | Version | Author name and designation | Summary of main changes |
|---|---|---|---|
| March 2023 | 1.0 | Hala Ghoz<br>Lead Protocols Pharmacist | New regimen protocol |
| April 2023 | 1.1 | Hala Ghoz<br>Lead Protocols Pharmacist | Indications for use updated |
| | | | |
| | | | |
| | | | |
| | | | |