Nivolumab (Opdivo®) single-agent

DRUG ADMINISTRATION SCHEDULE

Every 2-week schedule (all indications)

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nivolumab</td>
<td>240mg</td>
<td>IV infusion</td>
<td>Sodium chloride</td>
<td>60 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9% 100mL</td>
<td></td>
</tr>
</tbody>
</table>

Every 4-week schedule (melanoma & renal cell carcinoma)

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nivolumab</td>
<td>480mg</td>
<td>IV infusion</td>
<td>Sodium chloride</td>
<td>60 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9% 100mL</td>
<td></td>
</tr>
</tbody>
</table>

Cycle Length and Number of Days
An update to the dosing schedule and cycle period were published in May 2018 and this was approved by NHSE & CDF. All patients can now receive flat dosed treatment, and for melanoma & renal cell carcinoma can receive treatment every 4 weeks. As data becomes available the 4-weekly schedule may become part of the license for other indications.

Duration of treatment
- Hodgkin’s lymphoma, renal cell carcinoma - until disease progression or unacceptable toxicity.
- NSCLC and squamous cell carcinoma of head & neck – Every 14 days for up to 2 years of uninterrupted treatment or earlier in the event of disease progression.

APPROVED INDICATIONS
- NICE approved for;
  - Previously treated advanced renal cell carcinoma (RCC) in adults.
  - Relapsed or refractory classical Hodgkin lymphoma in adults after autologous stem cell transplant and treatment with brentuximab vedotin.
  - Advanced (unresectable or metastatic) melanoma in adults.
- Within the Cancer Drugs Fund;
  - As an option for treating locally advanced or metastatic squamous non-small-cell lung cancer (NSCLC) in adults after chemotherapy.
  - For locally advanced or metastatic non-squamous NSCLC in adults after chemotherapy if the patient's tumours are PD-L1 positive.
  - For treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy only if the disease has progressed within 6 months of having chemotherapy.

PREMEDICATION
Not routinely required.

RECOMMENDED TAKE HOME MEDICATION
Not routinely required unless specific toxicities require management.

INVESTIGATIONS / MONITORING REQUIRED
PD-L1 test (required for non-squamous NSCLC only).
FBC, U&E, LFT, including glucose and bicarbonate at baseline and before each dose. Any other testing as relevant to adverse events experienced (see toxicities section).
ASSESSMENT OF RESPONSE
Metastatic: Tumour size and patient symptomatic response.

REVIEW BY CLINICIAN
To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

ADMINISTRATION NOTES

**CAUTION**
Nivolumab administration can result in severe and fatal immune-mediated adverse reactions (irAEs). irAEs may involve gastrointestinal, endocrine, skin, liver, nervous, lung and other organ systems. Unless an alternate aetiology has been identified, signs and symptoms suggestive of irAEs must be considered inflammatory and Immunotherapy related. Early diagnosis and appropriate management are essential to minimise life threatening complications.
Systemic high dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe irAEs
It is recommended that all patients are given and advised to carry a Patient Alert Card for Immunotherapy (including after completion of treatment)

- Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with Nivolumab may occur at any time during or after discontinuation of Nivolumab therapy.
- Nivolumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
- Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.
- Use an infusion set with an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm)
- Patients should be given an alert card and be told to report any side effects

EXTRAVASATION  See NCA/Local Policy

TOXICITIES
Non-immune related
- Fatigue
- Pruritis and rash
- Diarrhoea
- Nausea
- Muscle pain
- Respiratory tract infections
- LFT derangement
- Reduced appetite
- Peripheral neuropathy

Immune related
- Pneumonitis
- Colitis
- Hepatitis
- Nephritis and renal dysfunction
- Endocrinopathies (e.g. diabetes, thyroid dysfunction, hypophysitis, adrenal insufficiency)
- Skin toxicities
Patient on Atezolizumab, Ipilimumab, Nivolumab or Pembrolizumab

In hours contact local acute oncology service or oncology day unit*
Out of hours contact on-call oncology nurse or on-call oncology consultant*

Note May need to arrange admission of patient or transfer (if already admitted) in patient oncology/acute oncology bed.

Mild-moderate Toxicity

Investigations and supportive measures
Consider Prednisolone 1mg/kg/day
(Consult on-call oncologist*)

Persistent Moderate or Severe/Life Threatening Toxicity

Investigations and supportive measures
IV Methylprednisolone
2mg/kg/day
(Consult on-call oncologist *)
May need alternative immunosuppressive drugs

*Check local Trust arrangements for whom to contract
# DOSE MODIFICATION / TREATMENT DELAYS

<table>
<thead>
<tr>
<th>Immune-related adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-related pneumonitis</td>
<td>Grade 2</td>
<td>Withhold nivolumab until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete. Initiate corticosteroids at a dose of 1mg/kg/day methylprednisolone IV or oral equivalent. May resume nivolumab after corticosteroid taper. If there is no improvement, increase dose to 2 to 4mg/kg/day methylprednisolone IV or oral equivalent and permanently discontinue nivolumab.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue nivolumab. Initiate corticosteroids at a dose of 2 to 4mg/kg/day methylprednisolone IV or oral equivalent.</td>
</tr>
<tr>
<td>Immune-related colitis</td>
<td>Grade 2 or 3</td>
<td>Withhold nivolumab until symptoms resolve. Grade 2 – if persistent, manage with corticosteroids at a dose of 0.5 to 1mg/kg/day methylprednisolone IV or oral equivalent. Upon improvement, taper corticosteroid and resume nivolumab. If worsening or no improvement, increase corticosteroid dose to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent and permanently discontinue Nivolumab. Grade 3 – Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent. Upon improvement, taper corticosteroid and resume nivolumab. If worsening or no improvement, permanently discontinue nivolumab.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue Nivolumab. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent.</td>
</tr>
<tr>
<td>Immune-related hepatitis</td>
<td>Grade 2 elevation in AST, ALT or bilirubin</td>
<td>Withhold Nivolumab until values return to baseline, and corticosteroids are complete. If values are persistently high, give corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent. Upon improvement, taper corticosteroid and resume Nivolumab. If worsening or no improvement despite corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent and permanently discontinue Nivolumab.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 elevation in AST, ALT or bilirubin</td>
<td>Permanently discontinue Nivolumab. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent.</td>
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</tbody>
</table>
# Immune-related nephritis and renal dysfunction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Creatinine Increase</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or 3</td>
<td>Withhold Nivolumab until creatinine returns to baseline. Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent. Upon improvement, taper corticosteroid and resume Nivolumab. If worsening or no improvement, increase corticosteroids to 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent, and permanently discontinue Nivolumab.</td>
<td></td>
</tr>
<tr>
<td>4 (Grade 4)</td>
<td>Permanently discontinue Nivolumab. Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent.</td>
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</tr>
</tbody>
</table>

# Immune-related rash

<table>
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<tr>
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<th>Management</th>
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</thead>
<tbody>
<tr>
<td>3 (Grade 3)</td>
<td>Withhold Nivolumab until symptoms resolve and management with corticosteroids is complete. In severe rash, initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent. If immunosuppression with corticosteroids is used to treat an immune-related rash, a taper of at least 1 month duration should be initiated upon improvement.</td>
</tr>
<tr>
<td>4 (Grade 4)</td>
<td>Manage the same as grade 3, however permanently discontinue Nivolumab.</td>
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</tbody>
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# Immune-related endocrinopathies

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism, hyperthyroidism, hypophysitis (Grade 2 or 3)</td>
<td>Withhold Nivolumab until symptoms resolve and management with corticosteroids is complete.</td>
</tr>
<tr>
<td>Hypothyroidism, hyperthyroidism, hypophysitis, diabetes (Grade 4)</td>
<td>Permanently discontinue Nivolumab</td>
</tr>
</tbody>
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No dose adjustment is necessary for mild hepatic impairment. Nivolumab must be administered with caution in patients with moderate (total bilirubin > 1.5 x to 3 x the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 x ULN and any AST) hepatic impairment.

No dose adjustment is required in patients with mild to moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

**TREATMENT LOCATION**
Can be given at Cancer Centre or Cancer unit.
REFERENCES
1. Summary of Product Characteristics: Nivolumab (Opdivo®)  
2. Nivolumab for treating advanced (unresectable or metastatic) melanoma. NICE  
   technology appraisal guidance [TA384] Published date: 18 February 2016

Document Control

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>Nivolumab (Opdivo®) single-agent</th>
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<tr>
<td>Document No:</td>
<td>CRP-17-L028</td>
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<tr>
<td>Current Version:</td>
<td>1.1</td>
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<tr>
<td>Reviewer:</td>
<td>Chris Beck, Cancer Alliance Pharmacist</td>
</tr>
<tr>
<td>Date Approved:</td>
<td>04/09/2018</td>
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<tr>
<td>Approved by:</td>
<td>Steve Williamson, Consultant Pharmacist, Northern Cancer Alliance</td>
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<tr>
<td>Due for Review:</td>
<td>04/09/2021</td>
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<tr>
<td>Summary of Changes:</td>
<td>1.0 First Issue</td>
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<td>1.1 Updated indications, dose &amp; cycle length</td>
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