Nivolumab Ipilimumab Combination Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>Indication</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults*</td>
<td>C43</td>
<td>00431a</td>
<td>ODMS 9/10/2017</td>
</tr>
</tbody>
</table>

* NOTE: Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%). Before initiating treatment with the combination, consultants are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy.

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Nivolumab and ipilimumab are administered once every 21 days for the first 4 cycles. From cycle 5, nivolumab is administered as monotherapy at either 240mg every 14 days (Ref NCCP Regimen 00483) or at 480mg every 28 days (Ref NCCP Regimen 00484) until disease progression or unacceptable toxicity develops.

For the monotherapy phase the first dose of nivolumab should be administered:

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240mg every 14 days; or
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480mg every 28 days.

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 therapy.

Facilities to treat anaphylaxis MUST be present when nivolumab is administered.

Cycles 1-4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>1mg/kg</td>
<td>IV infusion</td>
<td>Infuse over 30minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm</td>
<td>Every 21 days for 4 cycles</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>3mg/kg</td>
<td>IV infusion</td>
<td>0.9% sodium chloride to a concentration between 1 and 4mg/ml over 90min using a 0.2-1.2 micron low-protein binding in-line filter.</td>
<td>Every 21 days for 4 cycles</td>
</tr>
</tbody>
</table>

Nivolumab or Ipilimumab must not be administered as an intravenous push or bolus injection.

Nivolumab can be infused directly as a 10 mg/mL solution or can be diluted to as low as 1 mg/mL with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection.

*Vital signs including temperature, pulse and BP should be taken every 30mins for the duration of the infusion and 1 hour following completion of the infusion.

The line should be flushed with 0.9% sodium chloride after the ipilimumab infusion has finished.

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NC
CP
Chemotherapy Regimen

NCCP Regimen: Nivolumab Ipilimumab Therapy

Published: 09/10/2017
Review: 13/08/2020
Version number: 4

Tumour Group: Melanoma
NCCP Regimen Code: 00431

ISMO Contributor: Prof G Gullo, Prof M. Keane

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Please note that this regimen reflects the updated dosing posology for nivolumab from May 2018.

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Aged 18 years or above
- Adequate haematological, hepatic and renal function
- Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless prescribing consultant deems clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

EXCLUSIONS:

- Hypersensitivity to ipilumumab, nivolumab or any of the excipients
- Patients who have previously received treatment with PD-1/ PD-L1 inhibitors*
- Untreated symptomatic CNS metastases
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Patients with clinically significant autoimmune disease
- Symptomatic interstitial lung disease
- Any active clinically significant infection requiring therapy

*Prescribers should contact NCCP directly re patients who are intolerant to PD-1/PD-L1 inhibitors

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:
- Blood, liver and renal profile
- Glucose
- TFTs - TSH, free T3 and free T4
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- BRAF status
- PD-L1 expression using a validated test method

Regular tests:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>240mg</td>
<td>IV infusion</td>
<td>Infuse over 30minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm</td>
<td>Every 14 days ongoing to progression or toxicity</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>480mg</td>
<td>IV infusion</td>
<td>Infuse over 60minutes through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 μm</td>
<td>Every 28 days ongoing to progression or toxicity</td>
</tr>
</tbody>
</table>

Please note that this regimen reflects the updated dosing posology for nivolumab from May 2018.

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- Glucose
- TFTs - TSH, free T3 and free T4
- Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- BRAF status
- PD-L1 expression using a validated test method

Regular tests:
• Blood, liver and renal profile and glucose prior to each cycle
• TFTs - TSH, free T3 and free T4 prior to each cycle

Disease monitoring:
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:
• Any dose modification should be discussed with a Consultant
• Dose escalation or reduction is not recommended.
• If either nivolumab or ipilimumab is withheld, the other agent should also be withheld.

Ipilimumab
• Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of ipilimumab therapy and institution of systemic high-dose corticosteroid.
• Guidelines for withholding of doses or permanent discontinuation of ipilimumab are described in tables 1 and 2.

Table 1: When to withhold dose of ipilimumab

<table>
<thead>
<tr>
<th>Mild to moderate Adverse Reactions</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs</td>
<td>1. Omit dose until an adverse reaction resolves to Grade 1 or Grade 0 (or returns to baseline).</td>
</tr>
<tr>
<td>Hepatic: Grade 2 elevation in AST, ALT or total bilirubin</td>
<td>2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose.</td>
</tr>
<tr>
<td>Skin: Moderate to severe (Grade 3) skin rash or widespread/intense pruritus regardless of etiology</td>
<td>3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule.</td>
</tr>
<tr>
<td>Endocrine: Severe adverse reactions in the endocrine glands, such as hypophysisis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy</td>
<td>4. Discontinue ipilimumab if resolution to Grade 1 or Grade 0 or return to baseline does not occur.</td>
</tr>
<tr>
<td>Neurological: Moderate (Grade 2) unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)</td>
<td></td>
</tr>
<tr>
<td>Other moderate adverse reactions</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: When to permanently discontinue ipilimumab

<table>
<thead>
<tr>
<th>Severe Adverse Reaction</th>
<th>NCI-CTAE v4 Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)</td>
<td>Grade 3 or 4 diarrhoea or colitis</td>
</tr>
</tbody>
</table>
Hepatic:  
Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity  

<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 pneumonitis</td>
<td>Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 pneumonitis</td>
<td>Permanently discontinue treatment</td>
</tr>
<tr>
<td>Immune-related colitis</td>
<td>Grade 2 diarrhoea or colitis</td>
<td>Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete</td>
</tr>
<tr>
<td></td>
<td>Grade 3 diarrhoea or colitis</td>
<td>Withhold dose(s) until symptoms resolve</td>
</tr>
</tbody>
</table>

Nivolumab  
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of nivolumab therapy and institution of systemic high-dose corticosteroid.
- If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use. Nivolumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy.
- Guidelines for withholding of doses or permanent discontinuation are described in Table 3 below.

### Table 3: Recommended Treatment Modifications for Nivolumab

<table>
<thead>
<tr>
<th>Immune-related adverse reaction</th>
<th>Severity</th>
<th>Treatment Modification</th>
</tr>
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<tbody>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Grade 3 diarrhoea or colitis</td>
<td>Withhold dose(s) until symptoms resolve</td>
</tr>
</tbody>
</table>

*NCI- CTCAE v4.

*Any other adverse reactions that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to withhold/discontinue ipilimumab should be based on severity.

*Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.

ULN = upper limit of normal
### NCCP Chemotherapy Regimen

#### NCCP Regimen: Nivolumab Ipilimumab Therapy

**Published:** 09/10/2017  
**Review:** 13/08/2020  
**Version number:** 4  
**Tumour Group:** Melanoma  
**NCCP Regimen Code:** 00431  
**ISMO Contributor:** Prof G Gullo, Prof M. Keane

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<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 4 diarrhoea or colitis</th>
<th>and management with corticosteroids is complete</th>
<th>Permanently discontinue treatment</th>
</tr>
</thead>
</table>

**Immune-related hepatitis**

- Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin
- Grade 3 or 4 elevation in AST, ALT, or total bilirubin

Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete

Permanently discontinue treatment

**Immune-related nephritis and renal dysfunction**

- Grade 2 or 3 creatinine elevation
- Grade 4 creatinine elevation

Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete

Permanently discontinue treatment

**Immune-related endocrinopathies**

- Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency
- Grade 3 diabetes

Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present

Permanently discontinue treatment

**Immune-related rash**

- Grade 3 rash
- Grade 4 rash
- Steven-Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN)

Withhold dose(s) until symptoms resolve and management with corticosteroids is complete

Permanently discontinue treatment

**Other adverse reactions**

- Grade 3 (first occurrence)
- Grade 3 myocarditis
- Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day

Withhold dose(s)

Permanently discontinue treatment

---

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4)

### Renal and Hepatic Impairment:

#### Table 4: Dose modification of nivolumab and ipilimumab in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>No specific dose adjustment is necessary in patients</td>
<td>Administer with caution in patients with</td>
</tr>
</tbody>
</table>

### Table 4: Dose modification of nivolumab and ipilimumab in renal and hepatic impairment

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**ISMO Contributor:** Prof G Gullo, Prof M. Keane  
**Page:** 5 of 11
NCCP Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Severe</th>
<th>Has not been studied</th>
<th>Moderate -Severe</th>
<th>Has not been studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Moderate</td>
<td>No dose adjustment necessary</td>
<td>Mild</td>
<td>No dose adjustment necessary</td>
<td></td>
</tr>
</tbody>
</table>

with mild to moderate renal dysfunction. transaminase levels ≥5 x ULN or bilirubin levels >3 x ULN at baseline.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

These medicinal products are subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

Ipilumumab

- **Immune-mediated adverse reactions:**
  - Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.
  - The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.
  - Ipilimumab should be permanently discontinued and systemic high dose corticosteroid therapy initiated for severe immune-mediated reactions. Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy and clinical chemistries evaluated including liver function tests and thyroid function tests at baseline and before each dose.
  - Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and ipilimumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.
  - Management of immune-related adverse reactions may require high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Specific guidelines for management of Immune Mediated Adverse Events are available.

- **Infusion-related reactions:** Isolated cases of severe reaction have been reported. In case of a severe reaction, ipilimumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring.
Premedications with paracetamol and anti-histamine may be considered. Specific guidelines are available for the management of infusion-related reactions (2) and are detailed below.

**For mild symptoms:**
- For localized cutaneous reactions such as mild pruritus, flushing, and rash, decrease the rate of infusion until recovery from symptoms, remain at bedside, and monitor patient; complete ipilimumab or placebo infusion at the initial planned rate.
- Diphenhydramine 50 mg may be administered at the discretion of the treating physician.
- Patients may receive additional doses with close monitoring; premedication may be given at the discretion of the investigator.

**For moderate symptoms:**
- For any symptoms not considered mild or severe, eg, generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic blood pressure greater than 80 mm Hg, interrupt ipilimumab infusion, administer diphenhydramine 50 mg intravenously, remain at bedside, and monitor patient until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician. Resume ipilimumab infusion after recovery from symptoms.
- At the discretion of the treating physician, ipilimumab infusion may be resumed at one-half the initial infusion rate and then increased gradually to the initial infusion rate. If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab may be given with premedication (diphenhydramine and paracetamol and careful monitoring, following the same treatment guidelines outlined above.
- At the discretion of the treating physician, additional oral or IV antihistamine may be administered.

**For severe symptoms:**
- For any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema, the infusion of ipilimumab must be immediately discontinued.
- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV, as needed.
- Patients should be monitored until the investigator is comfortable that the symptoms will not recur. No further ipilimumab should be administered.
- In case of late-occurring hypersensitivity symptoms (eg, appearance within 1 week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

- **Patients with auto-immune disease:** Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.

**Nivolumab**

- **Cardiac adverse events and pulmonary embolism:** Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment.

- **Immune related adverse reactions:**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Withhold/</th>
<th>Recommended action -1st occurrence</th>
</tr>
</thead>
<tbody>
<tr>
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Immune-related pneumonitis
Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>(symptomatic)</td>
<td>Withhold, Permanent discontinuation</td>
</tr>
<tr>
<td>3 or 4</td>
<td></td>
<td>Permanent discontinuation</td>
</tr>
</tbody>
</table>

Immune-related colitis
Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>diarrhoea or colitis</td>
<td>Withhold, Permanent discontinuation</td>
</tr>
<tr>
<td>3</td>
<td>diarrhoea or colitis</td>
<td>Permanent discontinuation</td>
</tr>
<tr>
<td>4</td>
<td>diarrhoea or colitis</td>
<td>Permanent discontinuation</td>
</tr>
</tbody>
</table>

Immune-related hepatitis
Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>transaminase or total bilirubin elevation</td>
<td>Withhold</td>
</tr>
<tr>
<td>3 or 4</td>
<td>transaminase or total bilirubin elevation</td>
<td>Permanent discontinuation</td>
</tr>
</tbody>
</table>

Immune-related nephritis or renal dysfunction
Patients should be monitored for signs and symptoms of nephritis and renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or 3</td>
<td>serum creatinine elevation</td>
<td>Permanent discontinuation</td>
</tr>
</tbody>
</table>
### NCCP Chemotherapy Regimen

#### NCCP Regimen: Nivolumab Ipilimumab Therapy

| If worsening or no improvement occurs despite initiation of corticosteroids | Permanently discontinue | Upon improvement, nivolumab may be resumed after corticosteroid taper |
| Grade 4 serum creatinine elevation | Permanently discontinue | Increase corticosteroid dose to 1 to 2 mg/kg/day methylprednisolone (/equivalents) |

#### Immune-related endocrinopathies

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

| Symptomatic hypothyroidism | Withhold | Thyroid hormone replacement should be initiated as needed. |
| Symptomatic hyperthyroidism | Withhold | Antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized. |

#### Immune-related skin adverse reactions

| Grade 3 rash | Withhold | Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Rare cases of toxic epidermal necrolysis (TEN) some of them with fatal outcome have been observed. If symptoms or signs of Stevens-Johnson Syndrome (SJS) or TEN appear, nivolumab treatment should be discontinued and the patient referred to a dermatologist. |
| Grade 4 rash | Permanently discontinue | |

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**Tumour Group: Melanoma**

**NCCP Regimen Code: 00431**

**ISMOL Contributor: Prof G Gullo, Prof M. Keane**

This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoRegimens](http://www.hse.ie/NCCPchemoRegimens)

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The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer).
specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab, permanent discontinuation of nivolumab is recommended. Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immunestimulatory anticancer agents.

Other immune-related adverse reactions
For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld and corticosteroids administered. Upon improvement, nivolumab may be resumed after corticosteroid taper. Nivolumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

<table>
<thead>
<tr>
<th>Infusion reactions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate infusion reaction</td>
<td>Caution</td>
<td>May receive nivolumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.</td>
</tr>
<tr>
<td>Severe or life-threatening infusion reaction</td>
<td>Discontinue infusion</td>
<td>Administer appropriate medical therapy.</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS:
- No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. Since nivolumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting nivolumab or ipilimumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.
- Concomitant use of ipilimumab with anti-coagulants may increase risk of GI haemorrhage so close monitoring is required.
- Current drug interaction databases should be consulted for more information.

ATC CODE:
- Ipilimumab: L01XC11
- Nivolumab: L01XC17

COMPANY SUPPORT RESOURCES/Useful Links:
*Please note that this is for information only and does not constitute endorsement by the NCCP*

HCP Guide:
NCCP Chemotherapy Regimen

Patient Alert Card:
Ipilimumab:
Nivolumab:

REFERENCES:
2. Premedication and management of infusion reactions associated with ipilimumab administration. Bristol Myers Squibb Pharmaceuticals

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>09/10/2017</td>
<td></td>
<td>Prof G Gullo, Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>17/01/2019</td>
<td>Updated dose withholding and discontinuation criteria for ipilimumab for hepatic adverse reactions as per SmPC</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>18/06/2018</td>
<td>Updated inclusion criteria, baseline testing and dosing as per SmPC update</td>
<td>Prof G Gullo</td>
</tr>
<tr>
<td>4</td>
<td>18/7/18</td>
<td>Note added to indication on consideration of PD-L1 status &lt;br&gt;Revision of inclusion criteria to remove PD-L1 status</td>
<td>Prof G Gullo</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System <br>CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes <br>Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/

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