Durvalumab Monotherapy 1500mg – 28 Day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 ≥1% on tumour cells and whose disease has not progressed following platinum-based chemo-radiation therapy (CRT)	C34	00655a	ODMS 01/02/2021

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 patients individual clinical circumstances.

Durvalumab is administered once every 28 days until disease progression or unacceptable toxicity, or a maximum of 12 months (13 cycles).

Patients should commence cycle 1 within 42 days of completing chemoradiotherapy.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Durvalumab	1500mg	IV infusion	250ml NaCl 0.9% over 60mins using a low-protein binding 0.2-0.22 micron in-line filter.	Every 28 days
Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg. The final concentration of the diluted solution should be between 1mg/mL and 15mg/mL. Do not co-administer other medicinal products through the same infusion line.					

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

ELIGIBILITY:

- Indications as above
- Age ≥18 years
- ECOG 0 or 1
- Histologically- or cytologically-documented NSCLC with locally advanced, unresectable (Stage III) disease that has received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy. Patients must have received a total dose of radiation of at least 60 Gy
- Patients must have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.
- Adequate haematological, hepatic and renal function.

CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease
- Prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of organ transplant that requires therapeutic immunosuppression
- Patients with any grade pneumonitis from prior chemoradiation therapy

EXCLUSIONS:

- History of hypersensitivity to durvalumab or any excipient
- Prior exposure to any anti-PD-1 or anti-PD-L1 antibody
- Mixed small cell and non-small cell lung cancer histology
- Patients who receive sequential chemoradiation therapy for locally advanced NSCLC
- Patients with locally advanced NSCLC who have progressed whilst definitive platinum based, concurrent chemoradiation therapy
- 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)
- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- Any active clinically significant infection requiring therapy

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests
- Virology Screen:Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- PD-L1 expression using a validated test method

Regular tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests
- Virology Screen:Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C

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.
- Dose withholding or discontinuation may be required based on individual safety and tolerability. (Table 1)

Table 1: Dose modification of Durvalumab for adverse events

Adverse reactions	Severity[a]	Durvalumab treatment modification	Corticosteroid treatment unless otherwise specified
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1-4mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT > 5-≤ 8 x ULN or total bilirubin > 3- ≤ 5x ULN		
	Grade 3 with AST or ALT > 8 x ULN or total bilirubin > 5 x ULN	Permanently	

	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause	discontinue	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment.
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	

Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week	Withhold dose	Initiate 1-2mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2	Withold dose[b]	Initiate 2-4mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c]	Initiate 1-4mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	
Infection	Grade 3 or 4	Withhold dose until clinically stable	
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Consider initial dose of 1-4mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue[d]	

[a] Common Terminology Criteria for Adverse Events, version 4.03.

[b] If no improvement within 3 to 5 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which durvalumab can be resumed based on clinical judgment.

[c] Permanently discontinue durvalumab if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency

[d] For myasthenia gravis, if there are signs of muscular weakness or respiratory insufficiency, durvalumab should be permanently discontinued

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. After withhold, durvalumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤10mg prednisone or equivalent per day. Durvalumab should be permanently discontinued for recurrent Grade 3 or 4 (severe or life-threatening) immune-mediated adverse reactions.

For non-immune-mediated adverse reactions, consider withholding durvalumab for Grade 2 and 3 adverse reactions until ≤ Grade 1 or baseline. Durvalumab should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment)

Renal and Hepatic Impairment:

Table 2: Dose modification of durvalumab for renal and hepatic impairment

Renal impairment	Hepatic impairment
No dose adjustment of durvalumab is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population	Data from patients with moderate and severe hepatic impairment are limited. Due to minor involvement of hepatic processes in the clearance of durvalumab no dose adjustment of durvalumab is recommended for patients with hepatic impairment as no difference in exposure is expected

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal **(Refer to local policy)**

PREMEDICATIONS: None specified

OTHER SUPPORTIVE CARE:

Women of childbearing potential should use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details. **Durvalumab is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions**

- **Immune-mediated pneumonitis:** Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving durvalumab.

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and managed as recommended in table 1.

- **Immune-mediated hepatitis:** Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving durvalumab. Patients should be monitored for abnormal liver tests prior to and periodically during treatment with durvalumab, and as indicated based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in table 1.
- **Immune-mediated colitis:** Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving durvalumab. Patients should be monitored for signs and symptoms of colitis or diarrhoea and managed as recommended in table 1.
- **Hypothyroidism and hyperthyroidism:** Immune-mediated hypothyroidism and hyperthyroidism (including thyroiditis) occurred in patients receiving durvalumab, and hypothyroidism may follow hyperthyroidism. Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism and hyperthyroidism (including thyroiditis) should be managed as recommended in table 1.
- **Adrenal insufficiency:** Immune-mediated adrenal insufficiency occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in table 1.
- **Type 1 diabetes mellitus:** Immune-mediated type 1 diabetes mellitus occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in table 1.
- **Hypophysitis/hypopituitarism:** Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving durvalumab. Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in table 1.
- **Immune-mediated nephritis:** Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving durvalumab. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab and managed as recommended in table 1.
- **Immune-mediated rash:** Immune-mediated rash or dermatitis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving durvalumab. Events of Stevens- Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in table 1.
- **Other immune-mediated adverse reactions:** Given the mechanism of action of durvalumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions were reported in patients treated with durvalumab monotherapy in clinical trials: myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, encephalitis, Guillain-Barre syndrome and immune thromboctopenia. Patients should be monitored for signs and symptoms and managed as recommended in table 1. Events of pancreatitis have been reported in patients in

the clinical study programme. Patients should be monitored for signs and symptoms and managed as recommended for other immune-mediated adverse reactions, in table 1.

- **Infusion related reactions:** Patients should be monitored for signs and symptoms of infusion related reactions. Severe infusion related reactions have been reported in patients receiving durvalumab. Infusion related reactions should be managed as recommended in table 1.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab. Since the primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Durvalumab SmPC EMA. Last updated: 23/01/2020. Accessed: Jan 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/imfizi-epar-product-information_en.pdf
2. Antonia SJ et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018 Dec 13;379(24):2342-2350. doi: 10.1056/NEJMoa1809697.
3. Antonia SJ, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919-1929. doi: 10.1056/NEJMoa1709937.

Version	Date	Amendment	Approved By
1	11/2/2021		Prof Maccon Keane
2	31/03/2021	Updated management of adverse reactions and adverse effects in line with SPC updates.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.