Durvalumab

Indication

Locally advanced (Stage IIIA – IIIC), unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based concurrent chemoradiation.

Additional eligibility criteria:

- ECOG Performance status 0 - 1
- Patient has been re-staged since chemoradiotherapy was completed and does not have any evidence of disease progression or metastatic spread.
- Patient will start first treatment with durvalumab within 42 days of the last active treatment date of chemoradiotherapy.

(NICE TA578)

ICD-10 codes

Codes prefixed with C34

Regimen details

Day	Drug	Dose	Route
1	Durvalumab	10mg/kg	IV infusion

Cycle frequency

Every 14 days

Number of cycles

Until disease progression, unacceptable toxicity or for a maximum of 12 months.

It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Administration

Durvalumab is administered over 60 minutes, diluted in sodium chloride 0.9% or glucose 5%, to a final concentration of 1-15 mg/mL.

Durvalumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron filter.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions permanently discontinue treatment.

Emetogenicity

This regimen has low emetogenic potential

Additional supportive medication
Loperamide if required.

Extravasation
Durvalumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days

* every cycle for the first 12 weeks, then every other cycle.

Patients should be monitored for up to 5 months after last dose for adverse reactions.

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 3 x ULN

Dose modifications
Dose reductions are not recommended. Doses should be delayed or discontinued based on tolerability.

- **Haematological toxicity**

Discuss with the consultant if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

No dose modifications required in mild-moderate renal impairment (CrCl ≥ 30ml/min). There is limited data of use in patients with severe renal impairment - use with caution.

- **Hepatic impairment**

No modifications required for mild hepatic impairment (bilirubin < 1.0 x ULN, ALT/AST < 3 x ULN). See below for management of moderate – severe hepatitis.

- **Other toxicities**

Patients must be advised to seek specialist advice if they experience significant side effects as these can worsen rapidly.

Immune reactions may occur during or after completion of treatment.

Please refer to local guidelines for the management of immunotherapy toxicities.

For suspected immune related adverse events, durvalumab should be withheld and corticosteroids administered. Once symptoms have resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

Toxicity	**Definition**	**Dose adjustment**	**Corticosteroid treatment**
Pneumonitis	Grade 2	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 3-4	Permanently discontinue	Prednisolone 1-4mg/kg/day followed by taper
Hepatitis	Grade 2 Bilirubin 1.5-3 x ULN and/or AST/ALT 3-5 x ULN	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 3 Bilirubin 3-5 x ULN or AST/ALT > 5-8 x ULN	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 3-4 Bilirubin > 5 x ULN or AST/ALT > 8 x ULN	Permanently discontinue	Prednisolone 1-2mg/kg/day followed by taper
	Concurrent bilirubin > 2 x ULN and AST/ALT 3 x ULN and with no other cause	Permanently discontinue	Prednisolone 1-2mg/kg/day followed by taper
Colitis or diarrhoea	Grade 2	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 3-4	Permanently discontinue	Prednisolone 1-2mg/kg/day followed by taper

Hypothyroidism	Grade 2-4	No change	Thyroid replacement as clinically indicated
Hyperthyroidism	Grade 2-4	Withhold until clinically stable	Symptomatic treatment
Adrenal insufficiency Hypophysitis or Hypopituitarism	Grade 2-4	Withhold until clinically stable	Prednisolone 1-2 mg/kg/day followed by a taper and hormone replacement as clinically indicated
Insulin dependent diabetes mellitus	Grade 2-4	Withhold until clinically stable	Treat with insulin as clinically indicated.
Nephritis	Grade 2 (creatinine 1.5-3 x ULN or baseline)	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 3 (creatinine 3-6 x ULN or 3 x baseline) Grade 4 (creatinine 6 x ULN)	Permanently discontinue	
Rash	Grade 2 (> 7 days) or Grade 3	Withhold	Prednisolone 1-2mg/kg/day followed by taper
	Grade 4	Permanently discontinue	
Myocarditis	Grade 2	Withhold	Prednisolone 2-4mg/kg/day followed by taper
	Any Grade with positive biopsy Grade 3-4	Permanently discontinue	
Myositis/ polymyositis	Grade 2-3	Withhold	Prednisolone 1-4mg/kg/day followed by taper
	Grade 4	Permanently discontinue	
Infection	Grade 3-4	Withhold until clinically stable	
Other immune reactions	Grade 3	Withhold	Prednisolone 1-4mg/kg/day followed by taper
	Grade 4	Permanently discontinue	

If no improvement within 3 to 5 days despite corticosteroids, start additional immunosuppressive therapy as per local policy. Once resolved to Grade 0, corticosteroid taper should be initiated and continued over at least 1 month, after which durvalumab may be resumed based on clinical judgment.

Permanently discontinue treatment if adverse reaction does not resolve to ≤ Grade 1 within 30 days.

For non-immune-mediated Grade 2-3 adverse reactions, consider withholding treatment until ≤ Grade 1 or baseline. For any Grade 4 adverse reactions discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Colitis
Hepatitis
Peripheral neuropathy
Endocrinopathies
Nephritis
Interstitial lung disease/pneumonitis
Pancreatitis
Myocarditis

- **Frequently occurring side effects**

Infusion-related reactions
Pyrexia
Pruritus
Rash
Nausea and vomiting
Diarrhoea
Abdominal pain
Raised liver function tests
Fatigue
Decreased appetite
Hypo / Hyperthyroidism
Abdominal pain
Uveitis / Dry eyes
Myelosuppression
Myalgia / Myositis

- **Other side effects**

Adrenal insufficiency
Type 1 diabetes mellitus
Hypopituitarism
Hyperglycaemia
Tumour pain
Raised transaminases

Significant drug interactions – for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting durvalumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions.

Additional comments

The prescriber must discuss the risks of durvalumab therapy with the patient and provide the Patient Alert Card.

Contraception: Adequate methods of contraception should be used during therapy and for 8 weeks after last dose.

References

- National Institute for Health and Care Excellence TA 578 accessed 1 May 2019 via www.nice.org.uk
- Summary of Product Characteristics Durvalumab (AstraZeneca) accessed 3 April 2019 via www.medicines.org.uk
- Antonia SJ et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med 2017; 377:1919-1929 Antonia SJ et al. Overall survival with Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med 2018; 379:2342-2350

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