Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	Durvalumab in combination with chemotherapy for neo-adjuvant treatment and then continued as adjuvant monotherapy* for previously untreated stage IIA or IIB or IIIA or N2 only IIIB non-small cell lung cancer AND who are candidates for potentially curative surgery. NB: The patient either has been documented as NOT having a NSCLC which harbours an EGFR 19 or 21 mutation or an ALK gene fusion or the patient has a squamous cell carcinoma and a decision to not test for an EGFR 19 or 21 mutation or an ALK gene fusion and proceed with neoadjuvant durvalumab has been made following discussion at the Lung Cancer MDT and consideration of the relevant patient characteristics (including age and smoking status). Chemotherapy options for neoadjuvant component are: a 2-drug platinum-based combination with the platinum component being either cisplatin or carboplatin AUC 5 with either pemetrexed or paclitaxel or gemcitabine or vinorelbine. * i) if the patient has a resection, then post-operative radiotherapy or chemoradiotherapy can be given if indicated and in the absence of any progressive disease, the patient can proceed to adjuvant durvalumab. ii) if the patient does not have a resection, then radiotherapy or chemoradiotherapy can be given if indicated and in the absence of any progressive disease, the patient can proceed to adjuvant durvalumab iii) if the patient does not have surgery or radiotherapy or chemoradiotherapy, **no adjuvant durvalumab can be given.** iv) if there is disease progression during neoadjuvant or adjuvant durvalumab, no further anti-PD1 or anti-PDL1 immunotherapy is funded in any indication.
Treatment Intent	Neo-adjuvant followed by Adjuvant monotherapy which is intended to commence no later than 12 weeks after surgery. NB the intent is for the patient to commence adjuvant durvalumab monotherapy no later than 12 weeks after surgery. For any patient requiring any form of post-operative radiotherapy this is to start no later than 8 weeks after surgery and for adjuvant durvalumab to commence no later than 4 weeks after completion of radiotherapy.
Frequency and number of cycles	Neoadjuvant durvalumab with chemotherapy repeated every 21 days for a maximum of 4 cycles. Adjuvant durvalumab monotherapy repeat every 28 days for a maximum of 12 cycles. Durvalumab will be stopped sooner if there is any local or distant disease progression at any time in the neoadjuvant, peri-operative and adjuvant phases of treatment or unacceptable toxicity or withdrawal of patient consent. A formal medical review must be scheduled to take place by the end of the second cycle to review tolerance and whether to continue treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&Es, LFTs, blood pressure and random blood glucose (BM) at each cycle.

	• In combination with chemotherapy, refer to chemotherapy protocol for haematological parameters. Where these are not met, d/w consultant. • For durvalumab monotherapy, if PLT <75 or neuts <1.0 d/w consultant. • Thyroid function must be assessed at baseline then every 8 weeks or as indicated based on clinical evaluation. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose. • **Infusion-related reactions**: In the event of grade 3 to 4 infusion-related reactions, discontinue durvalumab and administer appropriate treatment. In the event of a mild or moderate reaction, interrupt or slow the rate of the infusion. Pre-medication for prophylaxis of subsequent infusion reactions should be considered. • The use of systemic corticosteroids or immunosuppressants before starting durvalumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions. Dexamethasone is permitted as prescribed within cytotoxic chemotherapy protocol. • **Renal impairment:** No dose adjustment is necessary in mild or moderate renal impairment. No data in severe impairment (<30ml/min). • **Hepatic impairment:** No dose adjustment is necessary. • **Dose modification**: *Patients with a body weight </=30 kg must receive weight-based dosing of 20mg/kg. • Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability. • **Adverse reactions** • **Immune-related reactions:** Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis / hypopituitarism, diabetes, immune-related rash. • For suspected immune-mediated adverse reactions, based on the severity of the adverse reaction, treatment should be withheld or permanently discontinued (See table 1 for Recommended treatment modifications and management recommendations for immune related reactions). Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and upon improvement to </= Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. • After withholding treatment, durvalumab can be resumed within 12 weeks if the adverse reactions improved to </= Grade 1 and the corticosteroid dose has been reduced to </=10 mg prednisone or equivalent per day. • Permanently discontinue for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. • For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • Non-immune-mediated adverse reactions, withhold treatment for Grade 2 and 3 adverse reactions until </= Grade 1 or baseline. • Discontinue in the event of 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).

	• Patients must be advised to contact the oncology team if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** No interaction studies have been performed.
References	KMCC protocol LUN-035 durvalumab SPC accessed online 13.12.24 CDF list V1.337 accessed online 13.12.2024

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 SPC Recommended treatment modifications and management recommendations for immune related reactions

Adverse reactions	**Severity**[a]	**Treatment modification**
Immune-mediated pneumonitis /interstitial lung disease	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis	ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN	Withhold dose
	ALT or AST > 5 - ≤ 10 x ULN	Withhold dose
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[b]	Permanently discontinue
	ALT or AST > 10 x ULN or total bilirubin > 3 x ULN	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose
	Grade 3	Withhold dose
	Grade 4	Permanently discontinue
Intestinal perforation[d]	Any grade	Permanently discontinue
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable
Immune-mediated hypothyroidism	Grade 2-4	No changes
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose
	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
	Grade 3	
	Grade 4	Permanently discontinue
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue
Immune-mediated myositis/polymyositis/rhabdomyolysis	Grade 2 or 3	Withhold dose[f]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose until clinically stable
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue
Immune-mediated Myelitis transverse	Any Grade	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Other immune-mediated adverse reactions[g]	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue

a Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value.
b For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.
c If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.
f Permanently discontinue IMFINZI if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
g Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, uveitis and cystitis noninfective.

NEO-ADJUVANT: In combination with chemotherapy, repeat every 21 day for 4 cycles: give durvalumab before chemotherapy

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		Stat **Only dispense when durvalumab given as monotherapy. When given in conjunction with chemotherapy, give antiemetics as per chemotherapy protocol.**
	DURVALUMAB	**1500mg *(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously. **Only dispense when durvalumab given as monotherapy. When given in conjunction with chemotherapy, give antiemetics as per chemotherapy protocol.**	

ADJUVANT: Monotherapy, repeat every 28 days to a maximum of 12 cycles.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	DURVALUMAB	**1500mg *(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	