Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	Serplulimab in combination with carboplatin and etoposide for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC). NB Previous treatment with concurrent chemoradiotherapy with / without maintenance durvalumab for limited stage SCLC is allowed as long as therapy was completed at least 6 months prior to the diagnosis of recurrent and extensive stage disease.
Treatment Intent	Palliative
Frequency and number of cycles	**Induction therapy:** Serplulimab in combination with carboplatin and etoposide every 21 days for 4 cycles. **Maintenance monotherapy** (in the absence of disease progression): Serplulimab monotherapy every 21 days until disease progression, unacceptable toxicity or withdrawal of patient consent, whichever occurs first.

Monitoring Parameters	• **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.
	• **Thyroid function** must be assessed at baseline then every 6 weeks or as clinically indicated.
	• **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 24 hours of the last steroid dose.
	• **Pre-treatment cardiac assessment:**
	  ○ **ECG** baseline, then every 6weeks or as clinically indicated.
	  ○ Check **BNP**, and **Troponin T** prior to treatment.
	• **EDTA / DTPA** or estimated CrCl (C&G) prior to cycle 1 must be >/= 30ml/min.
	• **Haematological monitoring and parameters:**
	• Monitor **FBC, U&Es, LFTs,** and **glucose** at each cycle.
	• **Cycles 1 – 4 (in combination with chemotherapy):**
	• If neuts >/=1.5 and PLT >/=100 continue with treatment. If neuts 1.0-1.4 and PLT >/=100 d/w consultant. If neuts <1.0 and/or PLT <100 delay treatment.
	• **Maintenance monotherapy Cycle 5 onwards**: If PLT <75 or neuts <1.0 d/w consultant.
	• **Hepatic impairment:**
	  ○ **Serplulimab**: No dose adjustment is needed for patients with mild impairment, bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST. There are insufficient data in patients with moderate impairment, bilirubin > 1.5 to 3 × ULN and any AST and no data are available in severe impairment, bilirubin > 3 × ULN and any AST, no dose recommendation can be made in moderate or severe hepatic impairment.
	  ○ **Carboplatin:** no dose adjustment required.
	  ○ **Etoposide:** Clinical decision. As a guide, if bilirubin 26-51 or AST 60-180 consider reducing dose by 50%.
	• **Renal impairment:**
	  ○ **Serplulimab:** No dose adjustment in mild or moderate (CrCL 30-89 ml/min) impairment. Insufficient data and no dose recommendation can be made in patients with severe (CrCL 15-29 ml/min) impairment.
	  ○ **Carboplatin:** If CrCl falls by >25% repeat / do EDTA to dose carboplatin. Discontinue carboplatin if CrCl <30ml/min.
	  ○ **Etoposide:** If CrCl </= 50ml/min consider dose reduction.

- **Infusion-related reactions:**
- **Serplulimab:**
  - Infusion-related reactions have been reported in patients receiving serplulimab. Patients should be monitored for clinical signs and symptoms of infusion-related reactions. Patients with Grade 1 infusion-related reactions may continue administration under close monitoring. The rate of infusion should be reduced, or treatment should be interrupted in patients with Grade 2 infusion-related reactions. Antipyretic and antihistamines may be considered. Treatment with serplulimab may be resumed under close monitoring when Grade 2 infusion-related reactions are controlled. For Grade >/=3 infusion-related reactions, infusion should be stopped immediately, treatment should be permanently discontinued.
- **Carboplatin:**
  - Mild/moderate reactions (grade 1-2): If symptoms resolve after treatment with hydrocortisone and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate.
  - If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be rechallenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment.
  - Severe (grade 3): Do not restart infusion. Consider alternative treatment.
  - Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment.
- **Adverse reactions**
  - **Serplulimab - 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 and corticosteroid administered, See table 1 for SPC Recommended treatment modifications and management recommendations for immune related reactions and the KMCC website.
  - Serplulimab must be permanently discontinued for **any Grade 4** and some specific Grade 3 immune-mediated adverse reactions.
  - For Grade 3, 4 and some specific Grade 2 immune-mediated adverse reactions (e.g. immune-mediated pneumonitis, immune-mediated myocarditis), corticosteroid (1-2 mg/kg/day prednisone or equivalent) and other symptomatic treatments should be given according to the clinical symptoms until recover or improve to Grade </= 1, corticosteroid taper should be initiated and continued over at least 1 month. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy (e.g., infliximab) should be added if there is worsening or no improvement despite corticosteroid use.
  - 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/
- **Dose Modification:**
  - **Serplulimab:** Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability see table 1.
  - **Carboplatin and etoposide:** d/w consultant if chemotherapy is delayed due to haematological toxicity. Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1.
- **Common drug interactions (for comprehensive list refer to BNF/SPC):**
  - **Serplulimab.** no formal drug interaction studies have been performed.
  - The use of systemic corticosteroids or immunosuppressants before starting serplulimab should be avoided. Steroids may be given as anti-emetics as part of this SACT protocol. Systemic

	corticosteroids or other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. ○ **Etoposide:** Ciclosporin (high doses) increases etoposide plasma levels/toxicity use with caution. ○ **Carboplatin:** Carboplatin: Caution with other nephrotoxic drugs • **Missed dose:** If a planned dose is missed, the next dose should be administered as soon as possible. The administration schedule must be adjusted to maintain a 3-week interval between doses. • **Pregnancy and contraception:** Women of childbearing potential should use effective contraception and not consider pregnancy during treatment and men should be advised to use effective contraception and not to conceive children during treatment, please refer to the brand specific SPC on carboplatin and etoposide for further guidance. • Women of childbearing potential should use effective contraception during treatment and for at least 6 months after the last dose of serplulimab. • **Driving and machinery:** patients should be advised to use caution when driving or operating machinery whilst receiving serplulimab. • Serplulimab contains polysorbate, which may cause allergic reactions. • Contains 0.98 mmol (or 22.5 mg) sodium per 10 ml (100mg) vial. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet. • Each patient should be given a copy of the HETRONIFLY ® patient alert card at each cycle.
References	UK-Hetronifly-SmPC-10mg_ml-concentrate for solution for infusion 20260304

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

Table 1 SPC Recommended treatment modifications and management recommendations for serplulimab immune related reactions		
Adverse reaction	Severity	Treatment modification
Immune-mediated lung disease	Grade 2	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Immune-mediated colitis	Grade 2 or 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Immune-mediated hepatitis	Grade 2 with AST or ALT > 3 to 5 times ULN, or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 with AST or ALT > 5 times ULN, or total bilirubin > 3 times ULN	Permanently discontinue
Immune-mediated nephritis and renal insufficiency	Grade 2 elevation of serum creatinine	Withhold until adverse reactions recover or improve to Grade 1
	Grade 3 or 4 elevation of serum creatinine	Permanently discontinue
Immune-mediated endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis, Grade 2 adrenal insufficiency, Grade 3 hyperglycaemia or type 1 diabetes mellitus	Withhold until symptoms resolve and management with corticosteroids is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 hyperglycaemia	Permanently discontinue
Immune-mediated skin reactions	Grade 3	Withhold until adverse reactions recover or improve to Grade 1
	Grade 4 Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue
Other immune mediated adverse reactions	Grade 2 myasthenia gravis / myasthenic syndrome* Grade 3 or 4 elevation of serum amylase or lipase Grade 2 or 3 pancreatitis Grade 2 myocarditis* Grade 2 or 3 other immune-mediated adverse reactions occurred for the first time Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Withhold until adverse reactions recover or improve to Grade 1
	Grades 3 or 4 myasthenia gravis / myasthenic syndrome Grade 4 pancreatitis or recurrent pancreatitis of any grade Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 4 other immune-mediated adverse reactions occurred for the first time Grade 4 or recurrent Grade 3 decreased platelet count (thrombocytopenia) or white blood cell count	Permanently discontinue
Infusion-related reactions	Grade 2	Reduce infusion rate to half rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).

Cycle 1 to 4 Induction therapy: repeat every 21 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	8mg	PO		
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	SERPLULIMAB	**4.5mg/kg**	IV	100ml /hr If the first infusion is well tolerated, all subsequent infusions may be given over 30 minutes	In Sodium Chloride 0.9% 100ml final concentration 1.0 to 8.0 mg/ml via in-line low-protein binding 0.22micron filter. Flush line after administration with 0.9% sodium chloride.
	CARBOPLATIN	**AUC 5** **Dose = AUC X (GFR + 25)** **(max 700mg)**	IV	30 minutes	In glucose 5% 500ml
	ETOPOSIDE	**100mg/m²**	IV	I hour	In Sodium Chloride 0.9% 500-1000ml (doses >200mg in 1000ml Sodium chloride 0.9%)
TTO	Drug	Dose	Route	Directions	
Day 1	**ETOPOSIDE**	**200mg/m² (max 400mg)** (round to the nearest 50 mg)	PO	OD on day **TWO** and **THREE** only. Take an hour before food or on an empty stomach.	
	Dexamethasone	6mg	PO	OM for 3 days with or after food	
	Metoclopramide	10mg	PO	TDS for 3 days, then 10mg up to 3 times a day when required. Do not take for more than 5 days continuously.	
	Ondansetron	8mg	PO	BD for 3 days.	
	Filgrastim	300micrograms or consider dose of 480 micrograms if patient >80kg	S/C	Daily from Day **3** to Day **7**	
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules only if required.	

Cycle 5 onwards Maintenance monotherapy repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	10mg	PO		
	SERPLULIMAB	**4.5mg/kg**	IV	100ml /hr If the first infusion is well tolerated, all subsequent infusions may be given over 30 minutes	In Sodium Chloride 0.9% 100ml final concentration 1.0 to 8.0 mg/ml via in-line low-protein binding 0.22micron filter. Flush line after administration with 0.9% sodium chloride.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 10mg pre-treatment dose) Do not take for more than 5 consecutive days. Dispense on **cycle 5** only if required.	