Cemiplimab (Cervical Cancer)

Indication
Recurrent or metastatic cervical cancer that has progressed on or after platinum-based chemotherapy

Regimen details

Day	Drug	Dose	Route
1	Cemiplimab	350mg	IV infusion

Cycle frequency
21 days

Number of cycles
Treatment should be continued until unacceptable toxicity or disease progression, for a maximum of 32 cycles

Administration
Cemiplimab is administered in 100mL sodium chloride 0.9% over 30 minutes. It must be administered via an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5-micron pore size).

Patients should be monitored for infusion related reactions, including nausea, pyrexia, abdominal pain, chills and flushing. For mild to moderate (Grade 1-2) reactions interrupt the infusion and recommence at a slower rate. For severe or life-threatening (Grade 3-4) reactions, permanently discontinue treatment.

Pre-medication
Nil

Emetogenicity
This regimen has low emetogenic potential

Additional supportive medication
Nil required routinely.

Extravasation
Cemiplimab is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per consultant instructions)
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
Luteinizing hormone	14 days
Follicle stimulating hormone	14 days
Testosterone	14 days
Troponin	14 days
CK	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	48 hours
U+E (including creatinine)	48 hours
LFT	48 hours
Calcium	As clinically indicated
Thyroid function*	48 hours every 6 weeks
Glucose	48 hours
Cortisol	48 hours every 6 weeks in gynae patients
Troponin	48 hours every 6 weeks in gynae patients
CK	48 hours every 6 weeks in gynae patients

*On alternate cycles.

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	≤2.5 X ULN or ≤5 X ULN with liver metastases. Contact Doctor if ALT / AST >70

Dose modifications

Dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

- **Haematological toxicity**

Discuss with the consultant if:
WBC <2.0 x 109/L
Neutrophils <1.0 x 109/L
Platelets <75 x 109/L

- **Renal impairment**

No dose adjustment is recommended for patients with mild – moderate renal impairment. There is limited data for cemiplimab in patients with severe renal impairment CrCl <30 mL/min – discuss with consultant.

- **Hepatic impairment**

No dose adjustment is recommended for patients with mild hepatic impairment. Cemiplimab has not been studied in patients with moderate or severe hepatic impairment.

- **Other toxicities**

Management of immune-related adverse reactions may require a dose delay or permanent discontinuation of treatment and initiation of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy. Dose reduction is not recommended.

Refer to UKONS and ESMO guidance for treatment of immune related toxicities.

Early identification and treatment is key.

<u>Permanently discontinue</u> treatment in patients with the following symptoms:

Toxicity – severe or life threatening	**Definition**
Pneumonitis	Grade 3 or 4 or recurrent grade 2 pneumonitis
Colitis	Grade 4 or recurrent grade 3 colitis
Hepatitis	Grade ≥3 with AST or ALT > 5xULN Or total bilirubin > 3xULN
Skin	Grade 4 or **confirmed** Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)
Nephritis	Grade 3 or 4
Other immune-related adverse reactions	– Grade 4 adverse reaction (excluding endocrinopathies) – Recurrent severe Grade 3 immune-related adverse reaction – Persistent Grade 2 or 3 immune-related adverse reactions lasting 12 weeks or longer (excluding endocrinopathies) – Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

<u>Withhold</u> treatment in patients with the following symptoms and refer to UKONS and ESMO guidance on treatment of immune mediated toxicities for full actions and advise:

Toxicity – severe or life threatening	**Definition**	**Action**
Pneumonitis	Grade 2	Withhold. Treat with initial dose of 1-2mg /kg/day prednisone or equivalent followed by a taper. Resume if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.
Colitis	Grade 2 or 3	Withhold. Treat with initial dose of 1-2mg /kg/day prednisone or equivalent followed by a taper. Resume if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.
Hepatitis	Grade 2 with AST or ALT >3 and ≤5xULN or total bilirubin >1.5 and ≤3xULN	Withhold. Treat with initial dose of 1-2/kg/day prednisone or equivalent followed by a taper. Resume if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper.
Hypothyroidism	Grade 3 or 4	Withhold if symptoms. Initiate thyroid hormone replacement as clinically indicated. Resume when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable.
Hyperthyroidism	Grade 3 or 4	Withhold if symptoms. Initiate symptomatic management as clinically indicated. Resume when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable.
Hypophysitis	Grade 2-4	Withhold if symptomatic. Resume if hypophysitis improves and hormone replacement is established.
Adrenal insufficiency	Grade 2-4	Withhold. Hormone (hydrocortisone) replacement should be commenced.

Type 1 diabetes	Grade 3 or 4	Withhold. Initiate treatment with anti-hyperglycaemics as clinically indicated. Resume when returns to Grade 0 to 1 or is otherwise clinically stable.
Skin	Grade 2 lasting longer than 1 week, Grade 3 or **suspected** Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold Treat with initial dose of 1-2 /kg/day prednisone or equivalent followed by a taper. Resume if improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.
Nephritis	Grade 2	Withhold Treat with initial dose of 1-2 /kg/day prednisone or equivalent followed by a taper. Resume if improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.
Other immune-related adverse reactions	Grade 2 or 3 clinical signs or symptoms of an immune- related adverse reaction not described above.	Withhold. Initiate symptomatic management, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper. Resume cemiplimab if immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.

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

- **Serious side effects**

Pneumonitis
Colitis
Hepatitis
Thyroid disorders
Hypophysitis
Adrenal insufficiency
Nephritis
Infusion related reactions
Vasculitis
ITP
Peripheral neuropathy, Guillain Barre syndrome, encephalitis

- **Frequently occurring side effects**

Skin disorders
Stomatitis
Diarrhoea
Fatigue
Arthralgia, arthritis
Decreased appetite
Hyperglycaemia
Abdominal pain
Anorexia

- **Other side effects**

Headache
Raised transaminases

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

Corticosteroids or immunosuppressants: use of systemic corticosteroids or immunosuppressants before starting cemiplimab, 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 cemiplimab to treat immune-related adverse reactions.

Additional comments

Patients must be provided with a Patient Alert Card before they start treatment.

Women of childbearing potential should use effective contraception during treatment with cemiplimab and for at least 4 months after the last dose of cemiplimab.

References

- Summary of Product Characteristics Cemiplimab https://www.medicines.org.uk/emc/product/10438/smpc
- NICE guidance: https://www.nice.org.uk/guidance/ta1174
- Survival with Cemiplimab in Recurrent Cervical Cancer N Engl J Med 2022;386:544-555

THIS PROTOCOL HAS BEEN DIRECTED BY DR YIANNAKIS, DESIGNATED LEAD CLINICIAN FOR GYNAE CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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