Amivantamab carboplatin pemetrexed

Indication

First-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations

Regimen details

Pemetrexed 500mg/m^2 intravenously
Carboplatin AUC5 intravenously
Amivantamab intravenously (see dosing schedule below under administration below)

Cycle frequency

Every 21 days

Number of cycles

Carboplatin is given for 4 cycles. Amivantamab and pemetrexed are given until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment

Administration

Patient must be prescribed dexamethasone 8mg BD to take for 2 days prior to the first dose of amivantamab.
Patient should be registered on the "Cocoon with you" support programme (provided by iQvia) to access skin care support.

Pemetrexed is given first followed by carboplatin then amivantamab

Pemetrexed

Pemetrexed should be administered first, followed by carboplatin
Pemetrexed is given in 100ml 0.9% sodium chloride over 10 minutes.

Carboplatin

Carboplatin is given in 500ml 5% dextrose over 30-60 minutes
Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of carboplatin.
Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, refer to the alliance protocol for management of hypersensitivity.

Amivantamab

Due to the frequency of IRRs at the first dose, amivantamab should be infused via a peripheral vein at Week 1 and Week 2; infusion via a central line may be administered for subsequent weeks when the risk of IRR is lower. It is recommended for the first dose to be prepared as close to administration as possible to maximise the likelihood of completing the infusion in the event of an IRR

Infusions should be interrupted at the first sign of IRRs of any severity and post-infusion medicinal products should be administered as clinically indicated. Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate. For recurrent Grade 3 or Grade 4 IRRs, amivantamab should be permanently discontinued

Body weight less than 80 kg*			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	33 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Week 4	1400 mg	125 mL/hr	
Subsequent weeks	1750 mg	125 mL/hr	
Body weight greater than or equal to 80 kg*			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1400 mg	25 mL/hr	50 mL/hr
Week 2	1750 mg	65 mL/hr	
Week 3	1750 mg	85 mL/hr	
Week 4	1750 mg	125 mL/hr	
Subsequent weeks	2100 mg	125 mL/hr	

*Dose adjustments not required for amivantamab for subsequent weight changes

†Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

Pre-medication

Two days before the first infusion:

During the two days prior to the initial amivantamab infusion, patients should receive 8 mg dexamethasone orally, twice daily (this will also serve as the premedication for pemetrexed)

Day of infusion:

On the day of the initial infusion (Week 1, Day 1), patients should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to intravenous dexamethasone to further reduce the risk of IRRs.

Prior to infusion (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs (see table below). For subsequent doses, antihistamines and antipyretics are required to be administered. Glucocorticoids should also be re-initiated after prolonged dose interruptions. Antiemetics should be administered as needed.

Premedication	Dose	Route of administration	Recommended dosing window prior to amivantamab administration
Antihistamine*	Chlorphenamine (10 mg) or equivalent	Intravenous	15 to 30 minutes
Antipyretic*	Paracetamol (1000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid (prior to first dose)	Dexamethasone (8 mg)	Oral	60 minutes
Glucocorticoid (prior to first dose)	Dexamethasone (20 mg) or equivalent	Intravenous	60 to 120 minutes
Glucocorticoid (prior to second dose)	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes
* Required at all doses.			

Folic acid 400µg OD orally beginning 1-2 weeks prior to the first dose of pemetrexed continuing 3 weeks after the last dose of pemetrexed.
Vitamin B12 1000µg IM injection 1-2 weeks prior to the first dose of pemetrexed repeated every 9 weeks until 3 weeks after the last dose of pemetrexed.
Dexamethasone 4mg BD should be taken the day before, the day of and the day after treatment with pemetrexed (when steroids are not taken for amivantamab premedication, usually from cycle 2 onwards)

Emetogenicity

Moderately emetogenic (carboplatin)
Pemetrexed given alone has minimal emetogenicity

Additional supportive medication

See above for vitamin supplementation for pemetrexed
Prophylactic skin management is recommended (COCOON trial):
Weeks 1-12: tetracycline antibiotic e.g., doxycycline or minocycline 100 mg PO TWICE daily.
Week 1 onwards while receiving treatment: apply a ceramide-based emollient cream to all skin ONCE daily, and apply a chlorhexidine 4% solution to nails ONCE daily and wash off during showering to prevent paronychia (provided by iQvia)
Week 13 onwards while receiving treatment: apply clindamycin 1% lotion to scalp ONCE daily after showering.

Instruct patient to limit sun exposure during treatment and for 2 months after

Extravasation

Pemetrexed is an inflammitant
Carboplatin is an irritant
Amivantamab is neutral

Investigations – pre first cycle

Standard pre-SACT investigations

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), calcium
ECG if clinically indicated

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	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 45 mL/min for pemetrexed See under Dose Modifications for adjustment of carboplatin dose
Bilirubin	≤ 1.5 x ULN
AST	<3 x ULN or < 5 x ULN in presence of liver metastases
Alkaline phosphatase	<3 x ULN or < 5 x ULN in presence of liver metastases

Dose modifications

Amivantamab dose modifications for adverse events (AE)

Dose level at AE occurrence	1050 mg	1400 mg	1750 mg	2100 mg
First dose reduction	700 mg	1050 mg	1400 mg	1750 mg
Second dose reduction	350 mg	700 mg	1050 mg	1400 mg

If further dose reductions required after 2nd dose reduction, discontinue amivantamab.

Haematological toxicity

If neutrophils < 1.5 x 10^9/L and platelets < 100 x 10^9/L delay for 1 week. If resolved then continue with 100% dose. If 2 or more delays then reduce doses of cisplatin/carboplatin and pemetrexed to 75%.

Renal impairment

Pemetrexed should NOT be administered if CrCl <45 ml/min
Carboplatin dose should be recalculated if the serum creatinine increases by >20% from baseline
Amivantamab: No dose reduction required in mild or moderate kidney dysfunction. This drug has not been studied in patients with severe kidney dysfunction.

Hepatic impairment

Pemetrexed: No information available for patients with bilirubin > 1.5 x ULN and/or AST/ALT > 3 x ULN (5 x ULN if liver metastases present) – consultant decision
Carboplatin: No dose modification required
Use amivantamab with caution, this drug has not been studied in patients with moderate or severe hepatic impairment.

Mucositis

Grade 3-4: reduce pemetrexed to 50% dose and continue with 100% dose carboplatin.

Neurotoxicity

Grade 2: reduce carboplatin to 50% dose and continue with 100% dose pemetrexed.
Grade 3-4: discontinue cisplatin/carboplatin.

Acneiform rash and paronychia	
Grade 1	Supportive care measures for symptomatic relief
Grade 2	Supportive care measures for symptomatic relief including topical corticosteroids and topical and/or oral antibiotics For poorly tolerated Grade 2, add systemic antibiotics and oral corticosteroids and consider dermatology consultation If rash does not improve after 2 weeks, consider dose reduction of amivantamab to the next lower dose level based on severity and reoccurrence
Grade 3	Supportive care measures for symptomatic relief as for poorly tolerated Grade 2, prompt referral to a dermatologist Withhold amivantamab until toxicity has resolved to Grade 0 to 2 Resume amivantamab at the next lower dose level If rash NOT resolved to Grade 0 to 2 within 2 weeks, permanently discontinue amivantamab
Grade 4	Permanently discontinue amivantamab

Interstitial lung disease (ILD) / pneumonitis	
Suspected ILD/ pneumonitis	Withhold treatment
Confirmed ILD/ pneumonitis	Permanently discontinue amivantamab

Any other grade 3-4 toxicity
Reduce carboplatin and pemetrexed to 75% of previous dose

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ototoxicity
Nephrotoxicity
Peripheral neuropathy
Interstitial lung disease
Ocular toxicity

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea
Oedema
Haematuria
Rash, pruritic

- **Other side effects**

Alopecia
Rash

Fatigue
Nail changes

Significant drug interactions

– for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose

Additional comments

References

Amivantamab SPC https://www.medicines.org.uk/emc/product/13084/smpc
Eviq guidelines: https://www.eviq.org.au/medical-oncology/respiratory/non-small-cell-lung-cancer-advanced-metastatic/4508-nsclc-locally-advanced-or-metastatic-carbopla#interactions
Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions Published October 21, 2023
N Engl J Med 2023;389:2039-2051

This protocol has been reviewed by Dr Lam consultant oncologist

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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