PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Ramucirumab and Gemcitabine

Malignant Pleural Mesothelioma

PROTOCOL REF: MPHARGMPM
(Version No. 1.0)

Approved for use in:

Malignant pleural mesothelioma progressing during or after first-line treatment with pemetrexed platinum doublet.

Not commissioned by NHSE

PS 0-2

Dosage:

Drug	Dose	Route	Frequency
Ramucirumab	10mg/kg	IV infusion	Day 1 ONLY of 21 day cycle
Gemcitabine	1000mg/m^2	IV infusion	Days 1 and 8 of 21 day cycle

To be continued until progression or unacceptable toxicity

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

Metoclopramide 10mg orally three times a day when required

Extravasation risk:

Ramucirumab- Neutral

Gemcitabine- Neutral

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Ramucirumab	No need for dose adjustment
	Gemcitabine	GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected Haemodialysis (HDx): no need for dose adjustment is expected. Start HDx 6-12 h after administration.

Hepatic	Ramucirumab	Mild hepatic impairment (total bilirubin >1.0-1.5 upper limit of normal (ULN) and any AST or total bilirubin ≤1.0 ULN and AST>ULN) or moderate hepatic impairment (total bilirubin >1.5-3.0 ULN and any AST)- proceed with treatment **Use with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome.** There are very limited efficacy and safety data available in these patients. Ramucirumab should only be used in these patients if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or*	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3

<table>
<tr><td></td><td></td><td>
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<tr><td>INR</td><td></td><td></td><td></td></tr>
<tr><td>Ascites</td><td>None</td><td>Mild to Moderate (diuretic responsive)</td><td>Severe (diuretic refractory)</td></tr>
<tr><td>Hepatic encephalopathy</td><td>None</td><td>Grade I–II (or suppressed with medication)</td><td>Grade III–IV (or refractory to medication)</td></tr>
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INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.
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<tr><td></td><td>Gemcitabine</td><td>Total bilirubin < 27 µmol/L: no dose adjustment is needed.
Total bilirubin ≥ 27 µmol/L: discuss with clinical team.
Options are:
Start at 80% of the original dose and increase the dose if tolerated.
OR
Start with full dose with active monitoring and/or follow-up.</td></tr>
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Interactions:

Please refer to the SmPC for full list of interactions.

Ramucirumab	No known drug interactions
Gemcitabine	Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Chlorphenamine	10mg	IV	30 minutes before chemotherapy
	Ramucirumab	**10mg/kg**	**IV Infusion**	**250mL sodium chloride 0.9% over 60 minutes (maximum infusion rate of 25 mg/minute via a non-pyrogenic line with a 0.2 micron filter)**
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**
8	Sodium Chloride 0.9%	250ml	IV Infusion	Flush
	Dexamethasone	8mg	Oral	30 minutes before chemotherapy
	Gemcitabine	**1000mg/m²**	**IV Infusion**	**250mL sodium chloride 0.9% over 30 minutes**

Repeated every 21 days until progression or unacceptable toxicity (at the discretion of the treating consultant).

Please NOTE: If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR) pre-medication must be given for all subsequent infusions; hydrocortisone 100mg IV and paracetamol 1g IV. The infusion rate of ramucirumab should be reduced by 50% for the duration of that infusion and all subsequent infusions.

Severe IRR, discuss with Consultant before continuing with treatment.

A heat pack can be applied throughout the **gemcitabine** infusion to relieve vein discomfort.
Gemcitabine is a radiation sensitizer: be aware if patients are also receiving radiotherapy.

Main toxicities:

Most Common Toxicities	
Grade 1-2	Grade 3-4
• Fatigue • Nausea and vomiting • Hypertension • Increase in transaminases (ALT and/or AST • Anaemia • Mucositis • Neutropenia • Diarrhoea • Thromboembolism • Thrombocytopenia • Bleeding • Proteinuria • Rash	• Neutropenia • Hypertension • Fatigue • Increase in transaminases (ALT and/or AST • Thrombocytopenia • Thromboembolism • Proteinuria • Febrile neutropenia

Ramucirumab therapy should be permanently discontinued in the event of:

- Severe arterial thromboembolic events
- Gastrointestinal perforations
- Severe bleeding: NCI CTCAE Grade 3 or 4 bleeding
- Spontaneous development of fistula
- Congestive heart failure
- Hepatic encephalopathy or hepatorenal syndrome

Investigations and treatment plan:

	Pre	Cycle 1		Cycle 2		Cycle 33		Ongoing
		D1	D8	D1	D8	D1	D8	
Informed Consent	x							
Clinical Assessment	x			x				Prior to cycle 2 then every 12 weeks or as clinically indicated.
OTR/Go-ahead	x			x		x		Prior to each treatment with Ramucirumab
SACT Assessment* (to include PS and toxicities)	x	x	x	x	x	x	x	Every cycle
FBC	x	x	x	x	x	x	x	Every cycle
U&E & LFTs	x	x	x	x	x	x	x	Every Cycle
Calculate GFR or Creatinine Clearance (CrCl)	x	x	x	x	x	x	x	Every cycle

Coagulation profile	x							At baseline in patients with conditions predisposing to bleeding (e.g. severe hepatic impairment, previous GI bleed/ulceration, dual antiplatelet therapy) and in those treated with anticoagulants and repeated as clinically indicated
CT scan	x							Every 3 months or if clinically indicated
ECG								If clinically indicated
Urinalysis**	x	x		x		x		Day 1 of each cycle
Full observations**		x	x	x	x	x	x	Every cycle
Weight recorded	x							Every cycle
Height	x							

*Refer to 'Main Toxicities' section for details on toxicities that require treatment discontinuation
** Refer to 'Non- Haematological toxicity' section

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 and 8 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0

Delay 1 week on day 1 and 8 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9

Blood counts and **coagulation parameters should be monitored** in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding.

On day 8 of the cycle **if blood results do not meet the above proceed rules then the day 8 dose will be OMITTED** and patient will proceed to the next cycle.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Infusion-related reactions

The infusion rate of ramucirumab should be reduced by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a grade 1 or 2 IRR. Ramucirumab should be immediately and permanently discontinued in the event of a grade 3 or 4 IRR.

Hypertension

Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled (usually by GP) before starting Ramucirumab treatment.

If diastolic increase > 20mmHg above baseline or blood pressure rises to >150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilized, is usually best managed via the patient's GP.

If blood pressure > 180/110mmHg, it is advised that Ramucirumab therapy is withheld until blood pressure controlled. If there is medically significant hypertension that cannot be controlled safely with antihypertensive therapy, Ramucirumab therapy should be permanently discontinued.

For "white coat syndrome" induced hypertension, please contact patient's GP for monitoring of blood pressure in between cycles.

Proteinuria

Patients should be monitored for the development or worsening of proteinuria during ramucirumab therapy.

1+ on Urinalysis (urinary protein <1.0 g/24 hrs)	**2+ or higher on Urinalysis** (urinary protein 1.0 - ≤ 3.0 g/24 hrs)
Continue with Ramucirumab. No additional evaluation required	<u>Ramucirumab therapy should be permanently discontinued if the urine protein level is >3 g/24 hours or in the event of nephrotic syndrome.</u> May have dose of Ramucirumab as scheduled, but will need 24 hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with treatment. With continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to < 1.0g/24hr, return to Urinalysis.

	If ≥2g, withhold Ramucirumab until repeat 24 hour urine collection shows < 2g protein. Then re-introduce Ramucirumab at a reduced dose level (see Table 1), with continued proteinuria monitoring via 24 hour urine. A second dose reduction (see Table 1) is recommended if a urine protein level ≥2 g/24 hrs recurs.

Table 1: Ramucirumab dose reductions for proteinuria

Initial ramucirumab dose	First dose reduction to	Second dose reduction to
10 mg/kg	8 mg/kg	6 mg/kg

Arterial thromboembolic events

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia have been reported in clinical studies. Ramucirumab should be permanently discontinued in patients who experience a severe ATE.

Gastrointestinal perforations

Ramucirumab is an antiangiogenic therapy and may increase the risk of gastrointestinal perforations. Cases of gastrointestinal perforation have been reported in patients treated with ramucirumab. Ramucirumab should be permanently discontinued in patients who experience gastrointestinal perforations.

Severe bleeding

Ramucirumab is an antiangiogenic therapy and may increase the risk of severe bleeding. Ramucirumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. For patients with evidence of portal hypertension or prior history of oesophageal variceal bleeding, screening for and treatment of oesophageal varices should be performed as per standard of care before starting ramucirumab treatment.

Impaired wound healing

In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld for at least 4 weeks prior to scheduled surgery. The decision to resume ramucirumab following surgical intervention should be based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, ramucirumab should be discontinued until the wound is fully healed

References:

1. SmPC for Ramucirumab 10 mg/ml Intravenous Infusion, Eli Lilly and Company Ltd – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated October 2021)
2. SmPC for Gemcitabine 38 mg/ml Concentrate for Solution for Infusion, Hospira- accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 11th February 2021).
3. Pinto, Carmine, et al. Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Oncology* 22.10 (2021): 1438-1447.

Circulation/Dissemination

Date added into Q-Pulse	16th March 2022
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
March 2022	1.0	**Hala Ghoz** **Lead Pharmacist for Protocols**	New Protocol Regimen V1.0