National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Eli Lilly and Company Limited	This is an appropriate topic. To date there are no licensed treatments for previously treated advanced gastric cancer making ramucirumab an innovative therapy for this patient group.	Comment noted
	Oesophageal Patients' Association	Yes	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Most definitely appropriate for NICE appraisal	Comment noted
Wording	Eli Lilly and Company Limited	Yes. We agree it is appropriate to appraise ramucirumab within its licensed indication for advanced gastric cancer or gastro-oesophageal junction (GOJ) adenocarcinoma previously treated with chemotherapy. Note: It is currently unknown whether ramucirumab will be licensed both as a monotherapy (JVBD) and/or in combination with paclitaxel (JVBE).	Comment noted

Section	Consultee/ Commentator	Comments	Action
		Lilly has submitted to the regulators data from both the REGARD trial (JVBD, Fuchs et al 2013) and the RAINBOW trial (JVBE, Wilke et al 2014).	
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes.	Comment noted
Timing Issues	Eli Lilly and Company Limited	Ramucirumab is expected to receive CHMP opinion at the end of September with licence expected in November 2014. Ramucirumab is expected to launch in the UK shortly after this date.	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Urgent as lack of guidance on standard treatment in this setting and a need to improve outcome for this setting.	Comment noted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Eli Lilly and Company Limited	This section provides comprehensive background information.	Comment noted
	Oesophageal Patients' Association	Good.	Comment noted

Section	Consultee/ Commentator	Comments	Action
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes but it is worth noting that not all patients who receive 1st line treatment for advanced disease will be suitable for further treatment so there is an attrition rate for second line treatment.	Comment noted
The technology/ intervention	Eli Lilly and Company Limited	As outlined in the description ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D) (Lu et al. 2003; Zhu et al. 2003).	Comment noted. The scope has been amended to state that ramucirumab prevents activiating ligands from interacting with VEGF-2 receptors.
	Oesophageal Patients' Association	Good.	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes.	Comment noted
Population	Eli Lilly and Company Limited	The appropriate population for this appraisal is patients with advanced gastric cancer or GOJ adenocarcinoma previously treated with fluoropyrimidine- and/or platinum-containing chemotherapy.	Comment noted. The population has been amended to 'Adults with advanced gastric cancer or gastro-oesophageal junction

Section	Consultee/ Commentator	Comments	Action
			adenocarcinoma previously treated with chemotherapy'. This population is in-line with the remit for this scope and broadly encompasses the two indications for ramucirumab.
	Oesophageal Patients' Association	Yes.	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes but they need to be of adequate Performance status in this case 0 or 1.	Comment noted. The scoping workshop attendees agreed that choice of treatment would not wholly be driven by performance status and therefore it was not appropriate to use it to define the patient population. No change to the scope required.
Comparators	Eli Lilly and Company Limited	To date there are no licensed second-line treatments for advanced gastric cancer. All active treatments are being used off label; resulting in significant variation in clinical practice. We agree that the identified comparators can be described as the 'best alternative care'.	Comment noted. The scoping workshop attendees agreed that comparators in the draft

Section	Consultee/ Commentator	Comments	Action
			scope were appropriate but that FOLFIRI should also be added because this is established clinical practice in England
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes.	Comment noted
Outcomes	Eli Lilly and Company Limited	Lilly agree with the proposed outcome measures.	Comment noted
	Oesophageal Patients' Association	Yes.	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes.	Comment noted
Economic analysis	Eli Lilly and Company Limited	The economic analysis will be conducted in line with the NICE reference case. A life time horizon will be used to reflect all the key differences between the relevant treatment options in terms of costs and effects.	Comment noted

Section	Consultee/ Commentator	Comments	Action
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Agree should be sufficiently long to compare.	Comment noted
Equality and Diversity	Eli Lilly and Company Limited	None have been readily identified.	Comment noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	No change required	Comment noted
Innovation	Eli Lilly and Company Limited	Ramucirumab is the first biologic to demonstrate single agent activity in the treatment of previously-treated advanced gastric and GOJ adenocarcinoma (REGARD, JVBD) compared to best supportive care. Ramucirumab in combination with paclitaxel is the first combination treatment shown to improve overall survival in previously-treated advanced gastric and GOJ adenocarcinoma patients (RAINBOW, JVBE). As discussed above, the current treatment pathway for previously treated advanced gastric cancer is not well defined as there are no licensed second line treatments. A robust clinical trial programme for ramucirumab has proven it to be an effective treatment as both a single agent and in combination with paclitaxel. This technology can provide meaningful health-related benefits to a very sick population who have no other approved options.	Comments noted. The company and other consultees will be able to fully describe why it considers ramucirumab to be innovative in their evidence submissions, which will then be considered by the Appraisal Committee

Section	Consultee/ Commentator	Comments	Action
		This represents a step change in clinical practice.	
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Yes it does have the potential to change management in this setting based on data from both the Regard trial and the Rainbow trial which evaluate ramucirumab alone or in combination with paclitaxel in this setting These data are from well conducted phase III trials. This could result in standard pathways for patients who relapse on first line treatment and in particular allow imaging and evaluation of these patients in the correct time frame to identify patients suitable for second line treatment. Providing second line treatment that is effective and improves symptoms and quality of life will impact on this disease and potentially end of life care and outcomes.	Comments noted. The company and other consultees will be able to fully describe why it considers ramucirumab to be innovative in their evidence submissions, which will then be considered by the Appraisal Committee
NICE Pathways	Eli Lilly and Company Limited	Based on the anticipated licence we would expect ramucirumab to fit under the 'gastric and duodenal cancer' section of the gastrointestinal cancer pathway. Under this section currently there is only guidance relating to Trastuzumab (TA208) and Capecitabine (TA191) for the first line treatment of gastric cancer and GOJ adenocarcinoma. There are currently no NICE clinical guidelines for gastric cancer.	Comment noted
Questions for consultation	Eli Lilly and Company Limited	*Would an original treatment regimen be used to re-challenge the disease if more than 6 months has passed since completing first-line treatment for advanced disease? If so, which treatment regimens would these be?* Re-challenge with first line treatment would not be considered for this patient population under consideration. Inclusion in the REGARD and RAINBOW trials required that patients had experienced disease progression ≤4 months after the last dose of first-line platinum and/or fluoropyrimidine containing chemotherapy for unresectable or metastatic disease.	Comments noted. The scoping workshop attendees agreed that re-challenge would only occur after disease progression, meaning it was not a comparator. However, it was noted that re-challenge did take place in routine clinical practice so the

Section	Consultee/ Commentator	Comments	Action
		Patients who received platinum-containing or fluoropyrimidine-containing adjuvant therapy were required to have progressed ≤6 months after the last dose (REGARD).	company should consider including this treatment strategy within its economic model.
	Eli Lilly and Company Limited	*Would taxanes or irinotecan be given as part of combination therapy for advanced disease previously treated with chemotherapy? If so, which combinations would be used?* The ESMO guidelines for gastric cancer recommend that in patients of adequate performance status, second-line chemotherapy is associated with proven improvements in OS and quality of life compared with best supportive care. The treatment options are cited as including irinotecan, docetaxel or paclitaxel. The supporting clinical trials referenced are for these treatments given as single agent (Waddell et al, 2013).	Comments noted. These monotherapies have been included in the scope. Additionally, scoping workshop attendees agreed that FOLFIRI should also be added to the scope as a comparator because this was more commonly used than irinotecan alone in established clinical practice in England
	Eli Lilly and Company Limited	*How should best supportive care be defined?* In UK clinical practice best supportive care (BSC) is likely to vary between patients receiving active second line treatment and those on BSC only. *REGARD Trial* BSC in the REGARD trial was defined as optimal supportive care measures, which may have included but were not limited to: anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, granulocyte-colony stimulating factors and erythroid growth factors. No concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational anti-cancer agents were allowed.	Comments noted. The scope has been updated to give examples of best supportive care in established clinical practice in England.

Section	Consultee/ Commentator	Comments	Action
		RAINBOW Trial In the RAINBOW trial, palliative and supportive care was administered for disease-related symptoms and treatment-related toxicity. These included, but were not limited to: antidiarrheal agents, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Palliative radiation was not permitted during either study. Active symptom control for patients in the control arm of the COUGAR-02 (Ford et al 2013) trial included: analgesics (including opioids), anti-emetics, steroids, palliative radiotherapy and any other supportive measures deemed appropriate by the clinicians treating the patients.	
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	1) All relevant comparators have been included in the scoping. 2) Yes an original treatment regimen can be used to re-challenge the disease and our own published data have demonstrated that any chemotherapy free interval of greater than 3 months is suitable for rechallenge in this setting: Rechallenge with platinum plus fluoropyrimidine +/- epirubicin in patients with oesophagogastric cancer. Okines AF1 et al Oncology. 2010;79(1-2):150-8. doi: 10.1159/000322114. Epub 2010 Dec 8. 3) Taxanes would usually be administered as monotherapy in this setting; irinotecan would usually be administered with 5FU as the FOLFIRI regimen. 4) Best supportive care changes across trials and settings but in this case is care from a multi disciplinary team that includes any intervention required for symptomatic relief other than chemotherapy (in this case including palliative oesophageal stent insertion) and also encompasses	1) Comment noted. Scoping workshop attendees agreed that FOLFIRI should be included as an additional comparator in the scope. The scope has been amended so that the comparator chemotherapies are not limited to those listed, which reflects the lack of a standard treatment option for this population. 2) Comment noted. The

Section	Consultee/ Commentator	Comments	Action
		psychosocial and spiritual needs as well as the physical needs of the patient. 6) Sub groups that benefit from ramucirumab –not identified in the multi - variate analysis in the trials but translational data are awaited. 7) Where it fits in the NICE pathway for gastrointestinal cancers - it is likely that gastric cancer and gastro-oesophageal junction cancer will need a separate box to duodenal cancer where guidance in this setting can be amalgamated with existing guidance for the currently available gastric cancer guidelines including both first and second line advanced setting recommendations.	scoping workshop attendees agreed re-challenge with first-line treatment would not be a comparator because the clinical trial inclusion criteria specified progression was within 4 months of completing first-line treatment (or within 6 months for adjuvant treatment) and that this was applicable to established clinical practice. 3) Comment noted. Scoping workshop attendees agreed that FOLFIRI should be included as an additional comparator in the scope 4) Comment noted. The scope has been updated to give examples of best supportive care in established clinical practice in England.

Section	Consultee/ Commentator	Comments	Action
			6) Comment noted. The scoping workshop attendees agreed that no subgroups could be defined at present 7) Comment noted
Additional comments on the draft scope	Oesophageal Patients' Association	Comments from clinical oncology specialists are more appropriate to the technicalities. Our patient's group is pleased to see that quality of life is listed in the 'Outcomes'	Comments noted
	Royal College of Physicians (on behalf of NCRI/RCP/RCR /ACP/JCCO)	Please clarify if the remit is for patients with performance status 1 and 0 only as in the trials to date. What level of existing peripheral neuropathy is allowed ie will this be defined in the population? Will patients who have had venous thromboembolism within 3 months and arterial thromboembolism within 6 months be excluded from the population as in the trials?	Comments noted. The Department of Health has provided NICE with a remit to appraise ramucirumab within its full marketing authorisation, which does not specify a minimum performance status or ineligibility because of thromboembolism. Any adverse effects of treatment would be expected to be captured by applying a disutility

Section	Consultee/ Commentator	Comments	Action
			within the company's economic model (whether this is for the technology being appraised or others in the treatment pathway).

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Health Improvement Scotland

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed:					
Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:

1.	Cochrane Upper Gastrointestinal and Pancreatic Diseases Group	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Cochrane Upper Gastrointestinal and Pancreatic Diseases Group has been added to the matrix of consultees and commentators under ' research groups'