National Institute for Health and Clinical Excellence
Health Technology Appraisal
Capecitabine for the treatment of advanced gastric cancer

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Roche	Yes	Comment noted. No action required.
	Royal College of Physicians	It is entirely appropriate that NICE reviews the role of capecitabine for advanced gastric cancer although the review should also cover advanced oesophago-gastric junctional (OGJ) and unresectable oesophageal cancer which are treated with the same chemotherapy regimens, based on the results of the pivotal REAL 2 trial. It would also be useful to address the role within peri-operative chemotherapy for resectable gastric and oesophago-gastric junctional cancer, as ECX is now the standard regimen in the NCRI and MRC's ST03 trial. The review could also be usefully expanded to compare oxaliplatin with the comparator, cisplatin, within combination chemotherapy for advanced oesophago-gastric cancer, based on the improved overall survival seen with EOX compared to ECF within the REAL 2 trial. This topic should certainly be referred to NICE for appraisal.	The appraisal will be carried out in accordance with the marketing authorisation of capecitabine, which does not include the use of capecitabine as peri-operative chemotherapy or for oesophago-gastric junctional cancer. No changes will be made to the scope. The possibility of expanding the appraisal to an MTA was discussed at the scoping workshop. The license of oxaliplatin does not include treatment of gastric cancer and consultees agreed that an STA would be the most timely and appropriate process.
	Royal College of Nursing	Yes, it would be timely and appropriate. Capecitabine has been shown to be effective in this disease group (REAL 2 trial)	Comment noted. No action required.
	Rarer cancers forum	It is very appropriate to do this there are patients who currently have an unmet need	Comment noted.
Wording	Roche	Yes	Comment noted. No action required.

Section	Consultees	Comments	Action
	Royal College of Physicians	Yes, although we think that "advanced" should be qualified as "advanced inoperable disease" and should encompass OGJ and oesphageal carcinomas also.	The text in the scope has been amended accordingly to include the term 'inoperable'. The appraisal will be carried out in accordance with the marketing authorisation of capecitabine, which does not include the use of capecitabine for oesophago-gastric junctional or oesophageal cancer. No changes will be made to the scope.
	Royal College of Nursing	When considering the aim of treatment (Background section) we would recommend that quality of life is added. This is an important consideration when giving palliative treatments. We would also add irinotecan to the list of regimens used. It may be used in second line treatment in certain cases.	The text in the scope has not been amended, as it is only intended to provide a brief summary of the condition. Effects on quality of life will be reviewed in the course of the appraisal. Irinotecan has not been added to the scope as this is for second line treatment; the remit of this appraisal is concerned with the first-line treatment of advanced gastric cancer.
	Rarer cancers forum	We fell that quality of life is a really important issue heer and how is that costed? Just comparing drug with drug does not take this into account	Comment noted. Quality of life will be taken into account in the course of the appraisal
Timing Issues	Roche	The timing for scoping workshop is fine, however suggested timing for the submisison of evidence is not appent in the covering email. Roche anticpate being in a posisiton to provide an evidence submission as early as in Q4 2009	The scope is not intended to provide a detailed timeframe for submission. If the topic is referred then all consultees and commentators will be informed in accordance with NICE method and process guides.
	Royal College of Physicians	Most centres are using capecitabine in place of infused 5-FU in advanced inoperable gastric, OGJ and oesophageal cancers following the presentation of the REAL 2 trial results. The ECX regimen is also replacing the ECF regimen used in the MAGIC trial for resectable gastric and OGJ cancers; extrapolating the non-inferiority demonstrated in the advanced disease setting to the resectable setting also. However, NICE approval would ensure that capecitabine is available to all patients; this is an important topic for appraisal.	Comments noted. No action required.

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	Royal College of Nursing	We would have appreciated a little longer to consider the draft remit and prepare a reply .	Consultees and commentators are given a designated 20 days for consideration of the draft remit and scope, in accordance with the NICE process guide (please see 'Guide to the technology appraisal process', section 3.3.1).
	Rarer cancers forum	This has been along term coming and is really really needed to extend lives.	Comment noted.
Additional comments on the draft remit	Roche	No comments	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Roche	Symptoms of gastric cancer additional to those listed are fatigue; dysphagia; early satiety; persistent vomiting; upper gastrointestinal bleeding.	Comments noted. The text in the scope has not been amended, as it is only intended to provide a brief summary of the condition.
	Royal College of Physicians	The wording is misleading where it states that patients with advanced disease have a 20% 5-year survival, as this neither reflects the survival of patients with resectable stage II-III disease, nor that of unresectable stage IV disease. The 5-year survival is approximately 36% for operable disease treated with surgery and peri-operative ECF chemotherapy, compared to a median survival of 9-11 months for advanced inoperable disease treated with palliative platinum-based combination chemotherapy, or 3 months if managed with supportive care alone.	Comments noted. The text in the scope has been amended accordingly.
	Royal College of Nursing	This section would benefit from the addition of appropriate references to support the information. When discussing the factors influencing survival we would add that existing comorbidities play a large part in how patients respond to treatment and ultimately the trajectory of their illness.	Comments noted. References are not added to the scope.
	Rarer cancers forum	We understand that this therapy is for advanced gastric adenocarcinmoa and not gastric squamous cell carcinoma or gastric lymphoma or gastric sarcoma or neuroendocrine gastric cancer this is not clear It is our understanding that gastric cancer can also be associated with alchol consumption and obesity this points are not noted	This was discussed at the scoping workshop. The population will reflect the licensed indication Comment noted. The text in the scope has been amended accordingly.
The technology/ intervention	Roche	Capecitabine (Xeloda, Roche) is an oral pro-drug that is PREFERENTIALLY converted to 5-fluorouracil (5-FU) in TUMOUR TISSUE not in the liver.	The text in the scope has been amended to reflect what is in the SPC.
	Royal College of Physicians	Capecitabine is metabolised in the liver but also undergoes further metabolism within the tumour itself, to become the active 5-FU.	The text in the scope has been amended to reflect what is in the SPC.
	Royal College of Nursing	Yes	Comment noted. No action required.

Section	Consultees	Comments	Action
	Rarer cancers forum	To our knowledge yes	Comment noted.
Population	Roche	Population is defined appropriately.	Comment noted, however the population has been amended to more clearly define the eligible patient population.
	Royal College of Physicians	"Advanced inoperable gastric cancer" would be more appropriate wording and should be expanded to include OGJ and oesophageal carcinomas and ideally, resectable gastric and OGJ cancers requiring the peri-operative chemotherapy approach (usually stage 1b and above).	Comment noted. The text in the scope has been amended accordingly to include the term 'inoperable'. The appraisal will be carried out in accordance with the marketing authorisation of capecitabine, which does not include the use of capecitabine as peri-operative chemotherapy or for oesophago-gastric junctional cancer. No changes will be made to the scope.
	Royal College of Nursing	This is appropriate	Comment noted, however the population has been amended to more clearly define the eligible patient population.
	Rarer cancers forum	It is our understanding that this for 95% of the gastric cancer populatiuon	Comment noted.
Comparators	Roche	We suggest that this section is more explicit about the comparitors of interest. We propose the following wording: "5-FU in combination with platinum-based chemotherapy regimens." These represent the majority of chemotherapy given in England and Wales for this indication.	Comment noted. This was discussed at the scoping workshop and the scope has been amended accordingly.
	Royal College of Physicians	Yes; but this should be qualified as infused 5-FU	Comment noted. This was discussed at the scoping workshop and it was agreed that it is not necessary to specify 'infused'. No changes will be made to the scope.
	Royal College of Nursing	5FU administered as a continuous infusion would be the standard comparator	Comment noted. This was discussed at the scoping workshop and it was agreed that it is not necessary to specify 'continuous infusion'. No changes will be made to the scope.

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	Rarer cancers forum	We understand that for some patients palliative surgery is given inorder to prevent blockage and control bleeding	Comment noted. This was discussed at the scoping workshop. The scope will not be amended as this treatment could form part of best supportive care, and could be given to both intervention and control groups.
Outcomes	Roche	Yes	Comment noted. No action required.
	Royal College of Physicians	Yes	Comment noted. No action required.
	Royal College of Nursing	Should we consider patient choice/satisfaction or would this be captured in health-related quality of life?	Individual choice and patient satisfaction is important for the NHS and its users. These factors will be taken into account during an appraisal, but they will not have the consequence of promoting the use of interventions that are not clinically and/or cost effective.
	Rarer cancers forum	Many of these patients will slowly starve to death patients with 20% of patients with upper GI cancer do so. We need to look at the quality of life with treatment survial is better nutrients can be taken and although the treatment is for extension of life (most patient at diagnosis have metatisised cancer due to poor early diagnosis in primary care) this must not be disregared	Comment noted. Quality of life will be incorporated into the framework of the appraisal.
Economic analysis	Roche	No comment	
	Royal College of Physicians	As the survival from advanced gastric cancer is so poor, a one-year gain in overall survival, progression-free survival or quality-adjusted life is not currently achievable.	Comment noted. The effects of capecitabine on overall survival, progression-free survival and quality adjusted life will be reviewed during the course of the appraisal. .
	Royal College of Nursing	No comment	Comments noted. No response required.
	Rarer cancers forum	We would like this to appoved quickly	Comment noted.
Equality and	Roche	No comment	Comment noted. No response required

Section	Consultees	Comments	Action
Diversity	Royal College of Nursing	All patients should be assessed individually, taking into account their ability to give informed consent to treatment, ability to be compliant with their medication, their preferred choice of treatment administration, and their physical status. If a language barrier is presented then an appropriate, impartial interpreter should be utilised.	Comment noted. Individual choice and patient satisfaction is important for the NHS and its users. These factors will be taken into account during an appraisal, but they will not have the consequence of promoting the use of interventions that are not clinically and/or cost effective.
	Rarer cancers forum	We know that stomach cancer happens more frequently to those who are social deprived and these people are often not offered the therapies or indeed the treatments that the affluent or offered It is also our understanding that some ethnic groups are more prone to develop this cancer	Comment noted. This was discussed at the scoping workshop. The scope will not be amended as these issues will not impede equality of access.
Other considerations	Roche	No comment	Comment noted. No response required
	Royal College of Physicians	We would strongly recommend that advanced OGJ and oesophageal cancers be included. Operable gastric and OGJ cancers requiring peri-operative chemotherapy (Stage 1b and above) could also be usefully covered by the appraisal. The substitution of oxaliplatin for cisplatin within triplet chemotherapy for advanced oesophago-gastric cancer should also be reviewed; the longest survival demonstrated in a phase III trial in a Western population was with a combination of epirubicin, oxaliplatin and capecitabine (EOX) within the REAL 2 trial. Oxaliplatin has a shorter infusion time then cisplatin and is less nephrotoxic. Also, oxaliplatin combinations were associated with lower rates of serious neutropaenia and thrombo-embolism than cisplatin combinations in the REAL 2 trial.	Comment noted. The appraisal will be carried out in accordance with the marketing authorisation of capecitabine, which does not include the use of capecitabine as peri-operative chemotherapy or for oesophago-gastric junctional cancer. No changes will be made to the scope. The possibility of expanding the appraisal to an MTA was discussed at the scoping workshop. The license of oxaliplatin does not include treatment of gastric cancer and consultees agreed that an STA would be the most timely and appropriate process.
	Royal College of Nursing	No comment	Comment noted. No response required.
	Rarer cancers forum	This therapy offers treatment with less toxity than the earlier drugs and thus is benifical to patients	Comment noted. Toxicity of capecitabine will be incorporated into the framework of the appraisal.

Section	Consultees	Comments	Action
Questions for consultation	Roche	We recommend the STA process should be utilised as the decision problem is whether Capectabine, a tablet formulation should replace the IV intravenous based treatment (5-FU) from within the existing current standard of care combination regimens for this patient group.	Comment noted. It has been recommended that an STA is the most appropriate process for this topic.
	Royal College of Nursing	The umbrella term 'inoperable gastric cancer' would cover the various stages of disease. The main first line treatments used in clinical practice have been identified. The options for this disease are limited. Radiotherapy is not an appropriate comparator as this is not a systemic treatment. No subgroups identified. The single technology process would appear to be the most suitable.	The text in the scope has been amended accordingly Comment noted. The text in the scope has been amended accordingly. Comment noted. Comment noted. It has been recommended that an STA is the most appropriate process for this topic.
Additional comments on the draft scope.	Roche	No comment	Comment noted. No response required

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Roche	Yes	Comment noted. No action required.

Section	Consultees	Comments	Action
Current or proposed marketing authorisation	Roche	Current indications for the technology: Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer. Xeloda is indicated for the treatment of metastatic colorectal cancer. Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. Planned indications for the technology Target dates for regulatory submission [redacted] Regulatory process followed [redacted] Anticipated date of CHMP positive opinion [redacted]. Commercial in confidence information [redacted]	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope
Welsh Assembly Government
Sanofi-Aventis

Royal Pharmaceutical Society
NHS Quality Improvement Scotland
Marie Curie Cancer Care
Macmillan Cancer Support