Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Comments submitted by [redacted], [redacted] on behalf of:

Name of your organisation: NCRI Upper GI Clinical Studies Group/RCP/ACP

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Oeosphago-gastric (OG) cancer represents an area of unmet need. Whilst the overall incidence of gastric cancer in the UK appears to be decreasing, that of junctional and lower oesophageal cancer is increasing (CRUK data) and incidence is higher in older patients. The UK's survival statistics for OG cancer compare poorly to those of other Western countries. Over 50% of patients present with advanced disease for palliative therapy. First-line platinum/fluoropyrimidine based chemotherapy (often as part of triplet therapy) is the standard first-line palliative chemotherapy associated with a median overall survival (OS) of 9-11 months in HER2 negative patients. For the sub-group of patients (approximately 20%) with HER2 amplification the addition of first-line trastuzumab to chemotherapy improves outcomes (NICE TA208 Nov 2010).

Ramucirumab, a fully human monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2), would be considered as monotherapy or in combination with paclitaxel for patients with progressive disease after first-line chemotherapy. Currently within the NHS, for patients of good performance status (range 30-50%), second-line palliative chemotherapy represents an evidence-based approach associated with an improvement in progression free survival (PFS) and OS as compared to best supportive care (BSC) alone. Across the UK second-line taxane use with either docetaxel or paclitaxel is widespread. Three weekly docetaxel may be used based on the results from the NCRI led COUGAR study in which docetaxel was associated with an improvement in median OS from 3.6 months to 5.2 months as compared to BSC with a hazard ratio (HR) of 0.67, p=0.01 (Ford et al, Lancet Oncology 2014). The COUGAR study also demonstrated an improvement in disease specific quality of life (QoL) in several domains. Weekly paclitaxel represents a well-tolerated alternative taxane utilised within the NHS and for which there are also level I evidence in the second-line treatment of advanced OG cancer along with irinotecan-based chemotherapy (Thuss-Patience PC EJC 2011, Kang JCO 2012, Hironaka et al, JCO 2013). In addition, for patients with a good progression free interval post first-line platinum therapy (i.e.>3-6 months), there is the option to re-challenge with the same first-line regimen.

If patients with relapsed oeosphago-gastric junctional tumours have received previous taxane therapy as part of a neo-adjuvant chemoradiation approach (based on the CROSS trial) or if patients have persistent peripheral neuropathy due to oxaliplatin use in the first-line, then irinotecan (with or without fluorouracil i.e. FOLFIRI regimen) may be used in preference of taxane in the second-line setting. There is clinical equipoise between weekly paclitaxel and three weekly docetaxel and the choice depends on physician and patient preference. However, weekly paclitaxel is a well-tolerated regimen and is used in multiple tumour types (i.e. breast and gynaecological cancers). If irinotecan is combined with fluorouracil (FOLFIRI

regimen), a central access venous device is required which is usually not the case with docetaxel or weekly paclitaxel. Treatment tolerance is an important consideration in this group of patients who can have multiple co-morbidities and are often of an older age.

As compared to the current standard second-line treatments, ramucirumab monotherapy represents a chemotherapy-free alternative to existing second-line options with a similar magnitude of OS benefit (3.8 months with BSC versus 5.2 months with Ramucirumab; HR 0.776, p-0.47) with relatively few side effects (REGARD trial; Fuchs et al, Lancet 2013). The HR for the improvement in PFS was 0.483. Ramucirumab is also given intravenously every two weeks so in terms of resource utilisation there is still MDU and chemotherapy chair/nurse time. However, the infusion duration is short (60 minutes). Importantly, ramucirumab appears to be well tolerated and the published data indicate that it was not associated with increased rates of fatigue, decreased appetite, vomiting, anaemia, or other toxic effects. The rates of any grade of adverse event were similar between the ramucirumab (94%) and placebo (88%) arms and of ≥grade 3 events were also similar between the two (57 and 58% respectively). Hypertension was predictably greater with ramucirumab. Despite a poor QoL return, there was no difference in global QoL health scores and median time to deterioration in ECOG performance status to ≥2 was longer for ramucirumab (5·1 months versus 2·4 months). Although there are no direct comparisons, it might be inferred that ramucirumab monotherapy potentially provides a less toxic alternative to chemotherapy in appropriate patients.

Importantly ramucirumab also improves OS and PFS when added to a weekly paclitaxel chemotherapy backbone. Median OS was 7.4 versus 9.6 months (HR 0.807, p=0.017) in favour of combination treatment (RAINBOW trial, Wilke et al, Lancet Oncology 2014). This was associated with a modest increase in grade ≥3 toxicity (neutropenia 41% vs 19%, leucopenia 17% vs 7%, hypertension 14% vs 2%, fatigue 12% vs 5%, anaemia 9% vs 10% and abdominal pain 6% vs 3%), although no increase in febrile neutropenia. The response rate was also higher with combination treatment (28% versus 16%) which in theory may provide additional benefit to patients with symptoms related to disease volume. Global QoL was not different between the two arms but more extensive QoL data will be presented in the future. The addition of intravenous ramucirumab to weekly paclitaxel does not increase the number of hospital attendances but does prolong the chair, nurse and pharmacy time on days 1 and 15 of every cycle. Weekly paclitaxel in combination with ramucirumab represents a new standard treatment for patients with advanced OG cancer and improves survival over and above the current chemotherapy alone approach for second-line therapy. This represents an important step forward for patients and the treatment of the disease.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

There may be geographic and ethnic variations in the underlying prognosis from advanced gastric and junctional adenocarcinoma between Western and East Asian

patients. In the RAINBOW trial, the median OS for the chemotherapy alone group was longer than in the Western second-line chemotherapy studies. However, in the sub-group of Western patients in RAINBOW, OS for paclitaxel alone was 5.9 months and that for Asian patients was longer at 10.5 months, consistent with previous studies where these respective ethnic groups predominate. The exact reasons are unknown but may relate to the greater use of post-progression (i.e. third and subsequent line) therapy in Asian patients and potentially to underlying as yet poorly characterised biological differences. However, in sub-group analysis in both REGARD and RAINBOW, all geographic groups appeared to derive benefit from ramucirumab and none were put at risk (i.e. detrimental survival) from the technology. In the Western sub-group (i.e. the group applicable to UK patients), median overall survival with paclitaxel plus ramucirumab was 8.5 months which represents a significant advance from historical survival figures in advanced OG cancer related to BSC alone (approximately 3 months OS) to chemotherapy alone (approximately 5 months OS) to now in excess of 8 months in the second line setting. This almost matches the OS figures reported in previous first-line studies.

RAINBOW and REGARD predated the routine use of first-line trastuzumab for advanced HER2 positive OG cancer and these patients would remain candidates for second line ramucirumab-based treatment. Depending on the results of on-going trials of HER2 targeted second-line therapy there may be alternative second-line options for patients with HER2 positive OG cancer in the future.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
In specialist oncology clinics.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
It is not available within the NHS.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
It should be noted that research into improving outcomes in advanced OG cancer through the first and now second/subsequent line therapy has greatly increased in the last few years and that further survival gains are unlikely to be achieved through chemotherapy alone. Targeted drugs have been widely investigated in the treatment of advanced OG cancer, with a particular increase in second-line evaluation. Targeting the epidermal growth factor receptor (EGFR), a successful approach in the lower gastrointestinal (GI) tract, has not so far translated into clinical benefit in OG cancer with drugs like cetuximab, panitumumab, erlotinib and lapatinib failing to demonstrate survival benefits in trials of unselected OG cancer patients. However, targeting the VEGF axis/angiogenesis has shown promise in advanced OG cancer. The global randomised phase III AVAGAST trial (Ohutsu JCO 2011) suggested a potential benefit in gastric/junctional tumours with an improvement in PFS and response rates in the group of patients receiving first-line chemotherapy in combination with bevacizumab. However, this failed to translate into a statistically significant OS advantage although there was a trend.

Both the REGARD (ramucirumab monotherapy) and RAINBOW (weekly paclitaxel plus ramucirumab) global randomised phase III trials show a statistically significant OS and PFS benefit favouring ramucirumab, validating an anti-VEGF/angiogenesis strategy in the treatment of advanced OG cancer and introducing another treatment option for these patients who have, hitherto, had limited treatment options. Apatinib, another anti-VEGF agent (oral tyrosine kinase inhibitor), appears to show efficacy in heavily pre-treated advanced OG cancer (Li et al, JCO 2013) and a randomised phase III double blind, placebo controlled study of apatinib versus BSC indicated an OS benefit in the third-line treatment of advanced OG cancer (Qin et al ASCO 2014), again validating VEGF/R targeting in this disease. The results from the ramucirumab studies herald a step change in the treatment approach to the OG cancer in terms of a second biologic agent demonstrating therapeutic activity (the first was trastuzumab), with others anticipated to follow in the future as distinct molecular subsets of patients continue to be defined. Currently, however, there appear to be no predictive biomarkers with clinical utility in the selection of patients for ramucirumab or other anti-VEGF agents such as bevacizumab.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
Both RAINBOW and REGARD recruited patients who had failed first-line chemotherapy (progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline) which is appropriate and reflects current practice for starting second-line chemotherapy. Treatment continued until disease progression (i.e. median duration of treatment in RAINBOW was 18 weeks for combination therapy versus 12 weeks for chemotherapy alone and PFS was 4.4 months and 2.9 months respectively) which also appears appropriate. Within the UK, patients having palliative chemotherapy

who reach 6 months of treatment are often offered or chose to have a treatment break as part of broader quality of life considerations. However, this might be a relatively small number given the PFS in the second-line setting. In REGARD, the median duration of treatment was 8 weeks versus 6 weeks for ramucirumab versus placebo and corresponding PFS was 2.1 versus 1.3 months. CT scans are standardly undertaken at 8 or 12 weeks during treatment within the NHS setting and are partly dependent on the patient's symptoms. They would not routinely be undertaken every 6 weeks as occurred within the trials (a requirement for accurate PFS data).

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

As discussed both REGARD and RAINBOW were global studies recruiting from a range of geographical locations and the OS benefit appeared to apply to all regions including Western patients, some of whom were recruited in the UK. The clinical trial results are applicable to UK patients and practice.

Overall survival was the appropriate primary endpoint and long term outcome to measure in both REGARD and RAINBOW and would be considered the gold standard endpoint in this setting. The other recorded secondary endpoints are standard for these randomised clinical trials and are similarly informative.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Please see answer to the first question where comparative toxicity and QoL data in both REGARD and RAINBOW are discussed. There are limited additional post marketing data regarding additional safety considerations. We are not aware of data from the compassionate access programme. All systemic anti-cancer agents are associated with toxicities. As a single agent monoclonal antibody, ramucirumab appears to be well tolerated. In combination with chemotherapy there is an improvement in patient outcomes with a modest increase in side effects. The favourable side effect profile of weekly paclitaxel as compared to some chemotherapy drugs and its widespread use are the main drivers to combine ramucirumab with paclitaxel. It is evident from several of the clinical trials now active or in development for second-line advanced OG cancer that weekly paclitaxel appears to be the preferred chemotherapy backbone on which to add novel targeted drugs.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No. All high quality sources of evidence have already been cited.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
The introduction of ramucirumab in combination with paclitaxel offers NHS patients with advanced OG cancer access to a more effective second-line treatment associated with superior survival than chemotherapy alone. The monotherapy option also offers an alternative to chemotherapy. In theory and drawing parallels with advanced colorectal cancer, the introduction of additional active evidence-based systemic options may eventually lead to a pathway of sequential therapies for patients with advanced OG cancer that translates to further improvement in survival.

The usual training and knowledge dissemination would occur at a trust-based level in terms of the introduction of a new cancer drug treatment. This would include review by trust-level formulary boards/ committees. Given that ramucirumab could only be prescribed in specialised oncology units/centres by personnel qualified to consent and administer chemotherapy, there are already robust processes to govern the safe introduction of a new therapeutic. The NHS already has significant experience with administering VEGF targeted and other monoclonal antibodies in the clinic (i.e. bevacizumab in advanced colorectal cancer) and there is a clear pathway for managing anti-VEGF specific toxicities such as hypertension and proteinuria. There would be no additional equipment or facilities required. As discussed, there may be

more frequent hospital attendance, nurse, pharmacy and MDU time for the combination treatment.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; No
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; No
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities. No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.