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Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your 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 statement, 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: Wasat Mansoor

Name of your organisation: Christie Hospital NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? No
- 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?

VARIATION IN PRACTICE

At relapse from first line chemotherapy, between 10% and 30% of patients are treated with further chemotherapy. The remaining 70-90% of patients are treated with best supportive care (BSC). There has been no landmark study looking at the variation in practice across the UK. However, there is data published in abstract form in ASCO 2015 (Astra M *et al*; J.Clin Oncol 33, 2015 (suppl 3; abst 184) which points to their being considerable variation in practice throughout the NHS (28% use docetaxel, 10% use paclitaxel, 7% use capectiabine, 7% use irinotecan, 9% use trastuzumab and the remaining 38% use various other drugs/combinations. In this study, 98% of the patients had a performance status (PS) of 0 or 1. The mean number of cycles given was 5.2.

Similar variations in use were also noted in market research done by the IPSOS Oncology Monitor on 2014 (46% use Docetaxel, 23% use paclitaxel, 2% use capecitabine and 8% use irinotecan). ** It is notable that in both these studies chemotherapy in 2nd line was only given in a very small minority of patient with a PS of 2 or higher.

DIFFERENCE IN EXPERT OPINION

Prior to 2014, there has been a large difference in opinion between professionals as to what should be regarded as the 'standard' 2nd line therapy. This has largely been due to very poor quality small studies that had been conducted. In 2014, a well conducted large study was published (Cougar02 (Ford *et al* Lancet Oncology 2013)). This demonstrated a modest benefit in favour of Docetaxel compared to placebo with respect to overall survival (OS) of 5.3 months vs 3.6 months (Hazard ratio 0.67). This was a statistically significant difference. The trial failed to demonstrate a difference in global QOL but there was an improvement in pain. This trial temporarily galvanised the professional body into accepting Docetaxel was the 2nd line standard of care. However, in 2015 the feeling is that practice is moving away from this back to the varied use of various agents. This reversal in practice has largely been due to the toxicity associated with docetaxel (especially myelosupression and peripheral neuropathy) and the very poor tolerability (especially for those patients with a PS of >=2). An additional important factor has been the exclusion of patients who have already developed peripheral neuropathy with 1st line chemotherapy (80% of patient on 1st line EOX chemotherapy develop peripheral neuropathy). Based on local practice in the Greater Manchester area and on 2nd opinions received from other networks, the real world experience

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with docetaxel in the 2nd line setting suggests docetaxel is becoming unpopular.

CURRENT ALTERNATIVE OPTIONS TO THE TECHNOLOGY

These have been listed above. The realistic alternatives are Docetaxel, irinotecan +/-5 FU analogue and paclitaxel

DOCETAXEL
Pros: Evidence base, reasonable schedule (3 weekly)
Cons: Excessive toxicity profile (peripheral neuropathy, myelopsupression (often requiring dose reduction, dose delays, supportive medication or in-patient admission), adverse impact on QOL (in the real world-based growing body of anecdotal evidence)
PACLITAXEL
Pros and cons: Similar to those for docetaxel however better tolerated than docetaxel. Also, weekly scheduling of paclitaxel has an impact on patients QOL/ freedom.
IRINOTECAN+/- 5FU ANALOGUE
Pros: some evidence to support activity: WJOG4007 Ueda *et al* 2012 compared 219 2nd line patients with paclitaxel or irinotecan. OS was 9.5 months (paclitaxel) vs 8.4 months (irinotecan). Difference was not statistically significant. Similarly, Thuss-Patience *et al* 2011 and Park *et al* 2011 compared irinotecan single agent vs BSC. Both trials demonstrated superior OS in favour of irinotecan – magnitude comparable to benefits seen for docetaxel in Cougar02.
Cons: No license for this use, toxicity profile can have an adverse effect on QOL (myelosuppression, anti-cholinergic toxicity)

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?

Molecularly, the only accepted sub-group with a different prognosis from the typical patient are those that are Her-2 positive. This cohort of patients will have received a trastuzumab containing regimen at 1st line. Those patients with a PS 2 or greater tend to have a much shorter life expectancy compared to the typical patient. They are more likely to succumb to the toxicity of chemotherapy.

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)?

As the therapy for gastric/GOJ cancers is given in a tertiary setting, the use of Ramucirumab would also be given in this setting. There would be no extra requirement for additional professional input.

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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?

The technology is currently not available

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.

There are currently no clinical guidelines for the use of 2nd line therapies.

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?

The main advantage of Ramucirumab compared to current alternatives is its superior toxicity profile with preservation of its superior efficacy (either as single agent or as a doublet). This is of utmost importance in this group of patients who have a very short median life expectancy. There is a reluctance in patients facing relapse of their cancer following 1st line treatment to undertake further therapy which is likely to offer them modest improvements in survival but jeopardize their QOL. The superior toxicity profile for Ramucirumab will make this a favoured choice for the majority of patients.

From the point of view of the clinician supervising the therapy, Ramucirumab given as single agent will require less intense supervision when compared to supervision required for the main alternative, Docetaxel. This is due to less Ramucirumab associated toxicity and better preservation of the patients' wellbeing/QOL. Toxicities in the REGARD study demonstrated similar rates of toxicity compared to BSC with the exception of hypertension.

From the nursing/administration perspective there are no major implications in the administration of Ramucirumab that sets it apart from current alternatives. As with all monoclonal antibody therapies, there is a requirement for pre-medication (chlorpheniramine) and the infusion is given over 60 minutes. The therapy is not dependent on biomarker testing.

When Ramucirumab is given as doublet in combination with paclitaxel, intensity of follow-up increases due to the addition of paclitaxel. Based on the Rainbow study the addition of paclitaxel to Ramucirumab generally increased toxicities but grade 3 toxicities were similar with the exception of hypertension. There was no impairment in QOL which highlights its ease of use.

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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.

The rules for starting /stopping Ramucirumab are generally similar to standard chemotherapy regimens. However, blood pressure and proteinuria while a patient is receiving Ramucirumab need to be monitored

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?

The two phase III trials that were done both reflect 'real world' clinical practice. The Regard study tested Ramucirumab against BSC. The clinical equipoise for comparing an agent against BSC in this setting was justifiable at the time the trial was being conducted. 70-90% of patients after relapse from 1st line therapy don't receive any active 2nd line therapy. This figure is very high because historically there has been a lack of evidence for 2nd line therapy, no licensing of agents for this indication and because patients performance status (PS) deteriorates rapidly post 1st line relapse. It was reasonable for the trial to exclude PS 2 patients as these patients are not likely to receive 2nd line treatment in the real world. The Rainbow study used single agent paclitaxel as its comparator arm. This was a reasonable comparator for the UK considering Cougar02 had not been published during Rainbow recruitment.

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?

As mentioned in previous questions, the relative lack of toxicity of Ramucirumab compared to alternative cytotoxic chemotherapy is a major strength of Ramucirumab. In the Regard study, grade 3 hypertension was more common in the Ramucirumab arm. Otherwise, all other toxicities were similar. From the Rainbow study, more grade 3 toxicities were observed in the combination arm (myelosupression but NOT neutropenic sepsis, fatigue, bleeding, peripheral neuropathy and hypertension). Real world experience suggests that hypertension and fatigue are the main issues with the doublet regimen. Resolution of hypertension using simple single agent hypertensive medication is straightforward. There are no toxicities that have emerged that are not discussed or listed in the two trials.

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Equality and Diversity

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;
- 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;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

No concerns about the above

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

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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.

Nil

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government 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 and the Welsh Assembly Government 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)?

More patients may receive single agent Ramucirumab than cytotoxic chemotherapy had Ramucirumab not been available. This is due to its superior safety profile. However, they would still need to have a PS 0 or 1. Therefore, I

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would anticipate that the numbers of patients receiving 2nd line single agent Ramucirumab therapy would increase but only modestly (limited by the PS). I would not anticipate this increase in numbers of people having 2nd line therapy would necessitate an additional resource. The use doublet therapy with Ramucirumab/paclitaxel should not increase the number of patients receiving 2nd line therapy. Cancer team throughout the UK are well practiced and educated in administering monoclonal antibody therapies. Therefore, there should be minimal or no extra training or education required in introducing this technology.