NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA307; Aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy

This guidance was issued in March 2014.

The review date for this guidance is August 2016.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of aflibercept in combination with irinotecan and fluorouracil-based therapy within its licensed indication for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy.

3. Current guidance

1.1 Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.

1.2 People currently receiving aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen should be able to continue treatment until they and their clinician consider it appropriate to stop.

4. Rationale[1]

Since the publication of TA307, no significant new evidence has been identified that is likely to lead to a change in the current guidance. It is therefore appropriate to transfer this guidance to the 'static guidance list'.

5. Implications for other guidance producing programmes

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

There is no proposed or ongoing guidance development that overlaps with this review proposal.

6. New evidence

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from December 2012 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

This review did not identify any new evidence that is likely to lead to a change in the recommendations of the original guidance.

The marketing authorisation for aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy has not changed since the previous guidance. The list price of aflibercept had not changed since the publication of TA307, that is, £295.65 for a 100 mg vial and £295.65 for a 200 mg vial. During TA307, the company agreed a confidential patient access scheme with the Department of Health that provided a simple discount to the list price of aflibercept. This was taken into consideration by the committee in TA307. There is no indication of a further discount being provided for afilbercept.

In TA307, the main uncertainty identified by committee wasthe company's extrapolation of overall survival beyond the trial (VELOUR) follow up period. The committee concluded that the extrapolation over 15 years did not provide a plausible mean overall survival benefit and was associated with great uncertainty. The literature review has not found any new evidence that is likely to resolve this uncertainty.

The literature review identified 3 post hoc analyses of VELOUR. One study, in a post hoc analysis of VELOUR, emphasised the treatment effect of aflibercept over placebo and suggested that this effect may be maintained over time but noted that the study was not powered enough to demonstrate a significant difference in overall survival at each time point. (Ruff *et al,* 2014). Two other studies, in perspective subgroup analyses, demonstrated that the treatment effect was maintained in certain subgroups. For example, in patients with or without prior bevacizumab treatment (Tabenero *et al*, 2014) and those of adjuvant fast relapses with a performance status 0 with any number of metastatic site or performance status 1 with <2 metastatic sites (Chau *et al,* 2014).

In summary, the new evidence is unlikely to lead to a change in the recommendation of the original guidance, given the uncertainties that remain with the extrapolation of overall survival and given the cost of aflibercept has not changed.

8. Adoption and Impact

No submission was received from the Adoption and Impact team.

9. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: Melinda Goodall, 11th July 2017

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (2012) NICE technology appraisal guidance 242

Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer (terminated appraisal) (2011) NICE technology appraisal guidance 240

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (2010) NICE technology appraisal guidance 212

Cetuximab for the first-line treatment of metastatic colorectal cancer (2009) NICE technology appraisal guidance 176

Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (2007) NICE technology appraisal guidance 118

Laparoscopic surgery for colorectal cancer (2006) NICE technology appraisal guidance 105

Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer (2006) NICE technology appraisal guidance 100

The use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003) NICE technology appraisal guidance 61

Colorectal cancer: diagnosis and management (2011 updated 2014) NICE guideline CG131. *Surveillance decision February 2016: "We will plan an update of the guideline on colorectal cancer (NICE guideline CG131). An extension to the scope of NICE guideline CG131 will be needed to cover areas covered by the guidance on improving outcomes in colorectal cancer (NICE guideline CSG5) that have not been superseded by other NICE guidance.*
We will withdraw NICE guideline CSG5 on publication of the update of the colorectal cancer guideline."
NB TA307 does not feature in the 2011 version of CG131 (understandably given the publication date), and in the 2014 update TA307 is referred to as 'related NICE guidance'.

Improving outcomes in colorectal cancers: manual update (2004) NICE guideline CSG5. *See the CG31 surveillance review decision February 2016, outlined above.*

Colorectal cancer (2012) NICE quality standard 20

Colorectal cancer (last updated April 2016) NICE pathway

In progress

Colorectal cancer (metastatic) - trifluridine (with tipiracil hydrochloride, after standard therapy. NICE technology appraisal guidance. Publication expected October 2016.

Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line). NICE technology appraisal guidance. Publication date to be confirmed. *1 Feb 16: "…The Committee felt that it did not have all the evidence and analyses necessary to make clinically meaningful recommendations, and we are considering what further analyses may be needed. We will therefore not issue an ACD or FAD at this point. We will provide an update once subsequent timelines are confirmed."*

Colorectal cancer (metastatic) - MABp1 (after previous treatments). NICE technology appraisal guidance. Publication expected February 2017.

Suspended/terminated

Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal) (2015) NICE technology appraisal 334

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"Aflibercept in combination with folinic acid/5-fluorouracil/irinotecan (FOLFIRI) (that is, in combination with irinotecan and fluorouracil-based therapy) has a UK marketing authorisation 'for the treatment of adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen'." "The manufacturer states that the net price of a vial of 100 mg aflibercept is £295.65, and the net price of a vial of 200 mg aflibercept is £591.30. The cost per patient will vary with dose adjustment and treatment duration. The manufacturer of aflibercept (Sanofi) has agreed a patient access scheme with the Department of Health that makes aflibercept available with a discount. The size of the discount is commercial in confidence."	The indication and net prices for 100mg and 200 mg remain unchanged.

Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Nintedanib (Boehringer Ingelheim) for metastatic colorectal cancer, second and subsequent line.	Phase III trials.	Yes, TS 8091 and ID1030 – at the scoping phase.

Registered and unpublished trials

Trial name and registration number	Details
NCT02045030 "A Phase II Exploratory Study to Identify Biomarkers Predictive of Clinical Response to Aflibercept in Patients With Metastatic Colorectal Cancer Who Have Failed First-Line Therapy"	Status: ongoing not recruiting. Number of patients: 52 Primary completion date: January 2016. *NB one of the inclusion criteria is: "Patients must have received only one prior chemotherapeutic regimen for metastatic disease. This prior chemotherapy must be an oxaliplatin containing regimen (in combination with bevacizumab). Patients who did not receive bevacizumab in their first-line treatment regimen may also be considered."*
NCT01571284 "Multicenter, Single Arm, Open Label Clinical Trial to Evaluate the Safety and Health-Related Quality of Life of Aflibercept in Patients With Metastatic Colorectal Cancer (mCRC) Previously Treated With an Oxaliplatin-Containing Regimen" (ASQoP)	Phase III Status: ongoing not recruiting Number of patients: 900 Primary completion date: June 2016 Primary objective: To provide metastatic colorectal cancer patients with access to aflibercept and to document the overall safety in these patients.

Relevant services covered by NHS England specialised commissioning

"Aflibercept - 2nd line in combination with irinotecan-based combination chemotherapy for metastatic colorectal cancer" was delisted on 12 March 2015 from the Cancer Drugs Fund.

References

Chau I, Joulain F, Iqbal SU et al. (2014) A VELOUR post hoc subset analysis: Prognostic groups and treatment outcomes in patients with metastatic colorectal cancer treated with aflibercept and FOLFIRI. *BMC Cancer* 14 (1): 605

Ruff P, Ferry DR, Lakomy R et al. (Jan. 2015) Time course of safety and efficacy of aflibercept in combination with FOLFIRI in patients with metastatic colorectal cancer who progressed on previous oxaliplatin-based therapy. *European Journal of Cancer* 51 (1): 18-26.

Tabernero J, Van CE, Lakomy R et al. (Jan. 2014) Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. European *Journal of Cancer* 50 (2): 320-331.