National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Masitinib for treating advanced or metastatic pancreatic cancer

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	AB Science	No comment	
	Royal College of Pathologists	*In response to the question 'Would it be appropriate to refer this topic to NICE for appraisal?'* Yes	Comment noted. No action required.
Wording	AB Science	No comment	Comment noted. No action required.
	Royal College of Pathologists	*In response to the question 'Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?'* Yes	Comment noted. No action required.
Timing Issues	AB Science	Filing to EMA is expected in Q3 2012	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	AB Science	The background information should be completed as follows: It should be emphasized that Mast cells impact overall survival in pancreatic cancer patients. Indeed, Tumor-infiltrating mast cells are associated with worse prognosis in pancreatic cancer. This finding is further corroborated by in vitro studies, which show that the interaction between mast cells and pancreatic cancer cells promotes growth and invasion. ➢ Inflammation around tumors potentiates cancer growth, especially that of pancreatic ductal adenocarcinoma (PDAC). [Esposito et al, 2004, Theoharides, 2008] ➢ Activation of Myc oncogene protein leads to rapid mast cell recruitment through CCL2 and mast cells are required for the angiogenesis and growth of pancreatic tumors. [Soucek et al, 2007] ➢ The number of mast cells increases with tumor progression, and mast cell infiltration into the tumor microenvironment is predictive of poor prognosis in patients with PDAC. [Chang et al, 2011] ➢ High mast cell counts in the intratumoral border zone of PDAC after curative resection were an independent prognostic factor for overall survival ($p < 0.001$). [Cai et al.] ➢ Mast cell infiltration was significantly increased in pancreatic cancer compared with normal pancreatic tissue (11.4 ± 6.7 versus 2.0 ± 1.4, $p < 0.001$). Furthermore, the mast cell count was shown to correlate with recurrence free survival; a high mast cell count (>13, n=18) being associated with a worse median recurrence-free survival (RFS) than patients with low mast cell count [8 vs. 16 months, $p<0.05$]. [Strouch et al, 2010].	The purpose of the background section of the scope is to briefly describe the current treatment pathway in the NHS and to contextualise the population, comparators and outcomes defined in the scope. The manufacturer will be able to describe the disease process, including cellular and molecular mechanisms, in its evidence submission. No change to scope required.

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		It should also be emphasized that Pain correlates with overall survival in pancreatic cancer patients, and Pain could be used as clinical factor to identify patients with advanced stage pancreatic cancer. ➢ Several studies have indicated a correlation between pain sensation and overall survival in pancreatic cancer patients [Andren-Sandberg et al, 1999; Watanabe et al, 2004; Lindsay et al, 2005]. ➢ Patients with back pain at time of prognosis of pancreatic cancer had a much poorer survival rate [Watanabe et al, 2004]. ➢ Pain usually correlates with advanced stage of pancreatic cancer. [Lindsay et al] ➢ The growth of tumor cells along nerves is a key feature of pancreatic cancer. [Abiatari et al 2008] ➢ The cardinal symptom of pancreatic cancer (abdominal pain often radiating to the back), as well as the high frequency of local tumor recurrence following resection, are both attributed to the unique ability of pancreatic tumor cells to invade the neuronal system.	
	Royal College of Pathologists	Perhaps mention that cure is not a likely outcome and that the drugs concerned are largely palliative.	The purpose of the background section of the scope is to briefly describe the current treatment pathway in the NHS and to contextualise the population, comparators and outcomes defined in the scope. No change to scope required.
The technology/ intervention	AB Science	The presentation of the technology should be completed as follows: Mastinib is a highly selective (Davis et al, Nat. Biotechnol. 2011) tyrosine kinase inhibitor that blocks specifically mast cells though the	The scope should only provide a brief summary of the mechanism of action of a technology. The manufacturer of

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		inhibition of c-Kit, Lyn, anf Fyn. Masitinib also blocks the platelet-derived growth factor receptor. In addition to this primary mechanism of action, masitinib exerts three additional mechanisms of actions ➢ Impact on anti-tumoral immune response: 1/ via dendritic cell (DC) mediated NK activation; 2/ via manipulation of macrophage regulators. ➢ Impact on development of metastasis via Wnt/ β -catenin pathway, via FAK pathway (through inhibition of Lyn and Fyn kinases), via inhibition of DDR1. ➢ Resensitization of resistant tumor cell lines in combination treatment.	the technology will be able to expand on the pharmacology in its evidence submission. No change to scope required.
	Royal College of Pathologists	Brief but accurate.	Comment noted. No action required.
Population	AB Science	Analysis in subgroups should be considered if such groups can be clinically or genetically characterised and masitinib can generate benefit on survival in such subgroups? Regardless of whether such subgroups have been predefined Especially, patients with pain at baseline, measured as VAS>20 is the subgroup which is most problematic because: - It has the poorest survival prognostic - Erlotinib is not efficacious in this subgroup Folfirinox has not generated any efficacy data in this subgroup	At the scoping workshop, consultees agreed that, if evidence allows, the following subgroups will be considered: locally advanced versus metastatic disease; level of pain (using an objective measure); presence or absence of biomarkers that could identify which patients are likely to experience a greater benefit of treatment. The scope has been amended to reflect this.
Comparators	AB Science	FOLFIRINOX is increasingly becoming a standard of care for good performance status patients.	Following discussion at the scoping workshop, consultees agreed that FOLFIRINOX was an appropriate comparator so this has been added to the scope.

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Outcomes	AB Science	No comment.	Comment noted. No action required.
	Royal College of Pathologists	*In response to the question: 'Will these outcome measures capture the most important health related benefits (and harms) of the technology?'* Probably	Comment noted. No action required.
Economic analysis	AB Science	No comment	Comment noted. No action required.
Equality and Diversity	AB Science	No comment	Comment noted. No action required.
Innovation	AB Science	No comment	Comment noted. No action required.
	Royal College of Pathologists	*In response to the question: 'Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?'* Possible but unlikely that it will represent a "step change" in management	Comment noted. No action required.
Other considerations	AB Science	No comment	Comment noted. No action required.
Questions for consultation	AB Science	No comment	Comment noted. No action required.

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

Marie Curie Cancer Care
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing