**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA/MTA)**

**Nanoliposomal irinotecan for treating pancreatic cancer after prior treatment with gemcitabine**

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

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness | Baxalta UK | Yes.<br>Pancreatic cancer is a condition associated with particularly high burden of illness and unmet need. In the UK the 1 year survival rate for all pancreatic cancer, is only 20% and the 5 year survival rate has only slightly improved from 2% in the 1970s to 3% in the last decade.<br>Patients with advanced disease in the post gemcitabine setting have even lower survival rates.<br>Furthermore, it has the lowest 1 and 5 year survival rates of all common cancers.<br>The technology represents a significant therapeutic advance for patients with locally advanced (non-resectable) or metastatic adenocarcinoma of the pancreas, where there has been little progress, especially in the post gemcitabine containing treatment setting. | Thank you for your comments. These comments will be taken into consideration by NICE and the Department of Health when deciding whether an appraisal is appropriate. |

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| | | Gemcitabine is the most commonly prescribed treatment option in England (SACT data), especially in first line treatment of this cancer, as well as the only NICE recommended therapy (TA25) | |
| | Pancreatic Cancer UK | Yes. There are very few treatments available to patients with advanced pancreatic cancer. Those that there are available are either extremely toxic, and therefore available to a very limited number of patients with a PS score of 0-1 (FOLFIRINOX), or generally lead to a poor response in patients (gemcitabine, where only about 10% of patients respond to treatment). Currently, there is no recognised standard of care for treating patients with Gemcitabine refractory pancreatic cancer. Given the limited treatment options open to this patient population, we need to see potential new advances appraised and decided upon as soon as possible. | Thank you for your comments. These comments will be taken into consideration by NICE and the Department of Health when deciding whether an appraisal is appropriate. |
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| Wording | Baxalta UK | No.<br>The anticipated wording for the licence is "[redacted]". This includes all treatment options containing Gemcitabine as monotherapy or in combination treatment | Thank you for your comments. The scope remit has been updated in line with the updated anticipated wording of the licence. |
| | Pancreatic Cancer UK | In terms of clincial effectiveness, note should be taken of the extremely short average survival time for metastatic pancreatic cancer patients following diagnosis, i.e. just 2-6 months. Thus even a small extension to survival time could represent a comparatively large percentage increase for patients and their families to benefit from. | Thank you for your comments. |

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| Timing Issues | Baxalta UK | A treatment option that has been shown to extend survival should be appraised by NICE as a priority, due to the following reasons:<br>• There are limited treatment options for patients with locally advanced non-resectable or metastatic pancreatic cancer post gemcitabine containing regimens;<br>• None of these current treatment options have undergone a NICE evaluation;<br>• These patients typically have a very short survival time. | Thank you for your comments. These comments will be taken into consideration by NICE and the Department of Health when deciding whether an appraisal is appropriate. |
| | Pancreatic Cancer UK | The lack of treatment options for pancreatic cancer, together with extremely poor prognosis - the worst of the 21 most common cancer - means any new treatment should be referred for appraisal with urgency. The proposed appriasal can therefore be regarded as urgent. | Thank you for your comments. These comments will be taken into consideration by NICE and the Department of Health when deciding whether an appraisal is appropriate. |
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**Comment 2: the draft scope**

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| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Baxalta UK | It is important to emphasise the draft scope statement that:<br>- "there is no consensus about the preferred treatment of patients with pancreatic cancer that have previously been treated with gemcitabine"<br>- "Capecitabine, Oxaliplatin & Irinotecan do not have marketing authorisation in the UK for treating pancreatic cancer"<br>In addition, none of these drugs have been appraised by NICE for this indication<br>We discuss the current treatment options in more detail in the "Comparator" section.<br>A relatively small number of patients go on to receive treatment after gemcitabine-containing regimens. | Thank you for your comments. The comparators section of the scope has been updated to reflect the treatment options currently used in clinical practice in the NHS. |
| | Pancreatic Cancer UK | This is generally a fair reflection of the situation, although it is also worth pointing out that five year survival rates for pancreatic cancer have remained below 5% for the past 40 years. Likewise there have been few new technologies put forward to treat the disease in the past couple of decades. Abraxane, one of very few new drugs put forward to treat pancreatic cancer was in 20 years, was recently rejected by NICE for use on the NHS and is soon to be removed from the Cancer Drugs Fund, leaving patients in England with even fewer treatment options. The poor treatment choice faced by pancreatic cancer patients should be taken into account when deciding whether or not to assess the new drug, as well as how quickly to carry out the assessment. | Thank you for your comments. These comments will be taken into consideration by NICE and the Department of Health when deciding whether an appraisal is appropriate. |
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| The technology/ intervention | Baxalta UK | Baxalta would suggest amending the sentence<br>"The nanoliposomes are expected to accumulate within the tumour and release the irinotecan slowly over time".<br>To be changed to:<br>The nanoliposomes are expected to accumulate within the tumour and release the irinotecan slowly over time, with higher tumour exposure to the active metabolite of irinotecan<br>We discuss our rationale in the "Innovation" section | Thank you for your comments. The technology section provides an overview of the technology and is not designed to provide an in-depth description. |
| | Pancreatic Cancer UK | It is worth highlighting that the trial referred to in the draft scope (D.Von Hoff et al., NAPOLI-1, 2014) found use of Nanoliposomal irinotecan with fluorouracil and folnic acid resulted in improved overall survival (6.1 months) compared to use of fluorouracil and folnic acid alone (4.2 months). It is of note that, in November 2014, the US Food and Drug Administration granted Nanoliposomal irinotecan plus flurouracil and folnic acid a Fast Track designation as a second-line treatment for patients with metastatic pancreatic cancer. A previous Phase II trial (A H Ko et al., 2013) demonstrated moderate antitumour activity with a manageable side-effect profile for metastatic, gemcitabine refractory pancreatic cancer. | Thank you for your comments. |
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| Population | Baxalta UK | Population: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in adult patients who have been previously treated with gemcitabine containing treatment.<br>No subgroups have been identified and will form part of the submission | Thank you for your comments. The scope population has been updated in line with the updated anticipated |

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| | | | wording of the licence. |
| | Pancreatic Cancer UK | Yes | Thank you for your comments. |
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| Comparators | Baxalta UK | Baxalta would like to strongly reiterate that there is currently no licensed product or NICE-approved therapy for metastatic pancreatic adenocarcinoma patients who have previously been treated with a gemcitabine-containing treatment.<br>**Gemcitabine + Capecitabine**:<br>Baxalta would advise against considering the combination of Gemcitabine +Capecitabine as a comparator.<br>Capecitabine alone is sometimes, though rarely, used in the setting. However, it is not used in combination with gemcitabine in patients who have already failed or are intolerant to gemcitabine.containing treatment regimens, so may be a stand-alone comparator.<br>Additionally, Capecitabine is a prodrug of 5-FU (5-fluoruracil) and generally considered to be therapeutically equivalent to infusional 5-FU (Xeloda SmPC 2015).<br><br>**Oxaliplatin + Fluorouracil:**<br>Baxalta agrees with considering Oxaliplatin + Fluorouracil containing treatments as a comparator.<br>In particular, the modified FOLFOX4 and 6 regimens, which consist of folinic acid (another name for Leucovorin), 5-Flourouracil and Oxaliplatin, though not | Thank you for your comments. The comparators section of the scope has been updated to reflect the treatment options currently used in clinical practice in the NHS. |

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| | | licensed or approved, are the most common treatment options in England for patients previously treated with gemcitabine-containing treatment.<br>**Folfirinox**:<br>Baxalta would advise removing this as a comparator for metastatic pancreatic patients who were previously treated with Gemcitabine-based therapies.<br>Although also not licensed, FOLFIRINOX is typically used in first line metastatic pancreatic cancer (for fit patients in preference to gemcitabine) and therefore should not be used as a routine comparator for patients who have already received gemcitabine-containing therapies. | |
| | Pancreatic Cancer UK | There is currently no recognised best standard of care for second-line treatment for advanced pancreatic cancer. Whilst FOLFIRINOX is considered best first-line treatment for advanced pancreatic cancer, it is not a standard second-line therapy and its high toxicity means it is only used on patients with a high Performance Status. In addition, we would question the inclusion of Gemcitabine plus Capcitabine. Although Capcitabine may be used as a second-line therapy for Gemcitabine refractory advanced pancreatic cancer, it would not be used in combination with Gemcitabine as Gemcitabine would not continue to be used in a patient who is unresponsive to it. There have been trials into FOLFIRI and irinotecan monotherapy as second-line treatments for advanced pancreatic cancer, but neither of these treatments are established practice so do not warrant inclusion. | Thank you for your comments. The comparators section of the scope has been updated to reflect the treatment options currently used in clinical practice in the NHS. |
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| Outcomes | Baxalta UK | Baxalta agrees that the listed outcomes are the most appropriate | Thank you for your comments. |
| | Pancreatic | Yes. It is important when considering overall survival to take account of the | Thank you for your |

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| | Cancer UK | poor prognosis given to pancreatic cancer patients, meaning even a slight extension to survival time is significant. Quality of life should not be limited to health-related outcomes. The impact of the treatment on a patient's social and emotional wellbeing, such as giving them longer to spend with their family, should also be taken into account. | comments. |
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| Economic analysis | Baxalta UK | It is important to recognise the lack of data where unlicensed medicines which have not yet been appraised by NICE are concerned, as stated in the Methods guide: "Specifically<br>when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use".<br>NICE should also recognise that this will also add to the uncertainty.<br>Patients in the post gemcitabine setting with metastatic pancreatic cancer do not, unfortunately, have an extended life expectancy, so any OS and other benefits are likely to be highly valued by these patients and society. | Thank you for your comments. |
| | Pancreatic Cancer UK | Any period of assessment, whilst being sufficiently long to pick up on differences in costs or outcomes, should also bear in mind that the average survival time for pancreatic cancer patients following diagnosis is just 2-6 months. | Thank you for your comments. |
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| Equality and | Baxalta UK | No | Thank you for your |

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| Diversity | | | comments. |
| | Pancreatic Cancer UK | NA | Thank you for your comments. |
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| Innovation | Baxalta UK | Yes.<br>The technology is innovative and represents a significant change in the management of this condition in the post gemcitabine containing treatments.<br>There is published evidence showing modified PK characteristics for nanoliposomal irinotecan in comparison to free-form irinotecan in the literature including slow clearance, extended plasma circulation, small volume of distribution and prolonged terminal half-life.<br>(Chang TC et al., Cancer Chemother Pharmacol 2015 epub ahead of print (doi 10.1007/s00280-014-2671-x),<br>(Roy AC et al. Ann Oncol. 2013;24(6):1567-1573)<br>In another clinical study, 72 hours after nal-IRI dosing, the total levels of irinotecan and its active metabolite, SN-38,were higher in tumor tissue than in plasma (Ramanathan RK et al. Proc.105th AACR; 2014. CT224.)<br>These studies demonstrate that nanoliposomal irinotecan results in higher exposure of the active metabolite of irinotecan in the tumour.<br>Many other development programs for a range of molecules have failed in this patient population, and therapeutic options therefore remain extremely limited.<br>Subsequently, the use of other off-label agents listed in the Comparator | Thank you for your comments. The innovative nature of nanoliposomal irinotecan will be considered by the Appraisal Committee if the topic proceeds to appraisal. |

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| | | section are based on lower levels of evidence than seen in many other indications.<br><br>This is exacerbated by the relatively short life expectancy and small patient numbers, especially in the post-first line setting, making trial recruitment, etc. challenging.<br><br>The anticipated life-extension provided by this technology would represent a significant improvement in survival for these currently underserved patients, and thus represents a step-change in the prognosis for patients with pancreatic cancer, especially in this advanced stage, post gemcitabine based treatment use. | |
| | Pancreatic Cancer UK | NA | Thank you for your comments. No action required. |
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| Other considerations | Baxalta UK | - | - |
| | Pancreatic Cancer UK | The appraisal should take account of the need to improve patient and clinical choice when it comes to treatment for pancreatic cancer. It should also be recognised that pancreatic cancer is a cancer of unmet need. Despite being responsible for over 5% of cancer death in England, the disease has the worst survival rate of the 21 most common cancers, with the five year survival rate having remained shockingly low (around 4%) over the past 40 years. Making available new treatments for the disease should therefore be treated as a matter of urgency. | Thank you for your comments. The comparators section of the scope has been updated to reflect the treatment options currently used in clinical practice in the NHS. |

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| Questions for consultation | Baxalta UK | **Comparators:** These have been addressed in the relevant section<br>**Subgroups**: No subgroups have yet been identified and will form part of the submission process<br>**Position in pathway:** Gemcitabine is already listed in this pathway. Nanoliposomal irinotecan would be positioned immediately after this treatment in the algorithm | Thank you for your comments. No action required |
| | Pancreatic Cancer UK | - | - |
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**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Department of Health
Eli Lilly
Pfizer
Roche
Royal College of Nurses
Royal College of Pathologists

**Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)**

The following organisations indicated that they had no comments on the provisional matrix of consultees and commentators

Baxalta UK
Department of Health
Eli Lilly
Pancreatic Cancer UK
Pfizer
Roche
Royal College of Nurses
Royal College of Pathologists