NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisal

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
Bloodwise	1- Although there are 'potential serious adverse affects' for people having idelalisib, we know there are often serious adverse effects associated from chemotherapy. People living with blood cancer may therefore tolerate the side-effects of idelalisib better than chemotherapy, in some cases. 2- We are disappointed that the data provided does not facilitate a reliable estimate of idelalisib's cost-effectiveness. However, we welcome NICE's proposals for the model to be improved. We hope that this could enable NICE to make a full assessment of its cost-effectiveness in future. 3- We do not agree with the decision not to recommend idelalisib on the NHS. We note, for example, the potential value of idelalisib as a treatment to the 'double-refractory' population, even if that benefit is only for a very short period of time, or the possibility that it could be used as a bridge to transplant. We therefore hope that the manufacturer will be able to provide sufficient further evidence to enable the treatment to be made available via routine commissioning.	Thank you for your comment. The appraisal consultation document (ACD) and final appraisal document (FAD) note that idelalisib and chemotherapy have different safety profiles and that idelalisib is generally well tolerated (see sections 3.2 and 3.21 of the FAD). The committee heard from the clinical experts that the different toxicity profiles for idelalisib and chemotherapy meant that people may not tolerate the specific adverse events of chemotherapy, but might tolerate those of idelalisib (section 3.3 of the FAD). The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect matching analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on

Consultee	Comment	Response
		variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and £86,161 per QALY gained) and because of its concerns with the quality of the evidence.
Lymphoma Action	1- Has sufficient consideration been given to the fact patients might prefer an oral therapy with possibly different side effects than more intensive chemotherapy after several treatments? 2- Has sufficient consideration been given to the different mechanism of action of idelalisib compared with chemotherapy, and the psychological advantage this offers patients who might be reluctant to undergo more chemotherapy after failing this type of treatment in the past? 3- Have frailer patients who are unable to have chemotherapy been given sufficient consideration?	Thank you for your comment. 1- Clinical experts explained that some patients may tolerate specific adverse events from idelalisib when they may not tolerate those from chemotherapy (see section 3.3 of the FAD). 2- The committee noted that idelalisib had a different mechanism of action to other available treatments, which might bring psychological benefits for people reluctant to have more chemotherapy after it had previously failed, but it was also aware that no evidence had been submitted to support this (see section 3.29 of the FAD). 3- Committee concluded that best supportive care is an option for those who cannot have chemotherapy, and it was therefore an appropriate comparator (see section 3.3 of the FAD). However, the committee was not presented with clinical data for best supportive care (sections 3.8 and 3.16

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		of the FAD)
Royal College of Pathologists/ British Society for Haematology	Thanks for these documents. They are extensive, detailed and give clear conclusions. My only comment is that the overall outcome is disappointing as this is an active agent that would be useful to use in some patients with difficult Follicular lymphoma and it's a shame that the non-randomised nature of the data sets assessed hasn't provided the adequate data necessary to enable access to this treatment.	Comment noted. The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and £86,161 per QALY gained) and because of its concerns with the quality of the evidence.

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Consensus of 15 clinical experts	Dear Sir / Madam, We are writing to encourage the NICE STA committee to approve the use of idelalisib in double refractory follicular lymphoma. Although follicular lymphoma is an indolent lymphoma with excellent survival for the majority of patients, it is increasingly recognised that there are a group of patients who have poor outcomes and will die of their disease. Much recent work has identified the so-called 'Progression of disease within 24 months of treatment initiation' or POD24 risk factor as a critical determinant for survival. For these patients the 5-year overall survival rate is only approximately 50%. This emphasises the consistent finding in follicular lymphoma that short remissions following R-chemo are associated with high risk disease. The 101-09 study (which included a significant number of patients from England) investigated idelalisib in a very high-risk group of patients – those who were refractory to both rituximab and an alkylating agent. As these patients were a high-risk relapsed group, one would expect them to be higher risk that the POD24 group described above, who were a group of patients at first relapse. They therefore represent a small group of patients with high unmet need. However, the long-term follow-up from the 101-09 study shows a median overall survival of 5 years which is much better than expected. Furthermore, the median PFS for the participants receiving idelalisib was longer than their prior line of treatment which is unusual in follicular lymphoma where remissions are usually thought to shorten with time. Furthermore, we collected the real-world results from UK patients treated with idelalisib when it was available on a named patient basis. Although the baseline characteristics of the patients were of course different from those in the 101-09 study, the results were very similar, suggesting that there was benefit outside of a clinical trial setting. We	Thank you for your comment. Within its decision making, the committee took into account the association of disease progression within 24 months of first relapse with an increased risk of death (see section 3.26 of the FAD), the improved overall survival of the latest DELTA (also known as 101-109 study) data cut (see section 3.5 of the FAD) and the comparison between DELTA and the real-world UK data (CUP) (see section 3.7 of the FAD). The committee noted that the company's decision not to pursue a confirmatory randomised controlled trial after DELTA had resulted in an important gap in the evidence base, making it more difficult to carry out an informed assessment of the effectiveness of idelalisib (FAD section 3.6). In the absence of head-to-head comparisons, the committee took into account the indirect analyses presented by the company. However, it identified a number of concerns with all indirect analyses (FAD sections 3.11 to 3.14), including sparse data, matching on variables defined differently (FAD section 3.13) and analyses that did not censor patients having a transplant (FAD section 3.8). The committee therefore agreed that the evidence presented by the company lacked robustness and concluded that idelalisib was not a cost-effective use of NHS resource because of the range of ICERs presented (between £16,481 and

Consultee	Comment	Response
	are also very concerned that England is the only country in Europe which cannot access this agent. Although we are aware NICE only covers England, there is clearly a UK wide inequality of access for this agent, which is of great concern as it seems deeply unfair that, for example, a patient living in Edinburgh can be treated with idelalisib whereas as a patient in Newcastle cannot be. We are very grateful for your time in reading this letter and considering our arguments. We are also very grateful for the excellent work of NICE and its committees.	£86,161 per QALY gained) and because of its concerns with the quality of the evidence. (FAD section 3.25).