

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Idelalisib for treating refractory follicular
lymphoma**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using idelalisib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using idelalisib in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 23rd October 2018

Second appraisal committee meeting: 6th November 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Idelalisib is not recommended, within its marketing authorisation, for treating follicular lymphoma that has not responded to 2 previous lines of treatment in adults.
- 1.2 This recommendation is not intended to affect treatment with idelalisib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

The options after 2 lines of treatment for follicular lymphoma include a range of chemotherapy treatments. The choice of the specific treatment depends on what the person has had already.

Idelalisib has not been compared directly with current chemotherapy treatments. So, it is unclear whether it is better, and if so by how much, than what the NHS currently offers.

It is therefore not possible to reliably estimate the cost effectiveness of idelalisib. Because of this, idelalisib cannot be recommended for routine use in the NHS or for inclusion in the Cancer Drugs Fund.

2 Information about idelalisib

Marketing authorisation indication	Idelalisib (Zydelig, Gilead) has a marketing authorisation 'as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment'.
Dosage in the marketing authorisation	Idelalisib is administered orally at a dose of 150 mg, twice daily. Treatment is continued until disease progression or unacceptable toxicity.
Price	The list price for idelalisib is £3,114.75 per pack of 60 150 mg film-coated tablets (excluding VAT, company submission). The company has a commercial arrangement for idelalisib, which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Gilead and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Treatment pathway

This appraisal focuses on idelalisib as a third-line treatment

3.1 The final NICE scope specified a population with follicular lymphoma that is refractory to 2 previous lines of therapy, that is, third-line treatment. This is in line with the marketing authorisation and the company's submission. The population considered in the appraisal is narrower than the population specified by the marketing authorisation. It relates to a 'double-refractory' population (that is, the follicular lymphoma did not respond, or only showed a limited response to at least 2 previous treatments) and the previous treatment had to include an anti-CD20 monoclonal antibody (rituximab or obinutuzumab) and chemotherapy containing an alkylating agent (for example, cyclophosphamide). Clinical experts considered this 'double-refractory' population to have an unmet need for treatment options. The committee agreed that the population presented in the company's submission was appropriate.

There is no single standard of care chemotherapy for the third-line treatment of follicular lymphoma

3.2 In the population who would be offered idelalisib (see section 3.1), most people are currently offered chemotherapy including (as listed in the NICE scope) cyclophosphamide- containing regimens, fludarabine-containing regimens, bendamustine and chlorambucil. The clinical experts explained that these vary in effectiveness and toxicity. The choice of chemotherapy regimen depends on individual circumstances, and takes into account previous chemotherapy use and clinician preference. Because of this, there is no single standard of care chemotherapy regimen in this population. The committee concluded that all the chemotherapeutic regimens listed in the scope were appropriate comparators.

Best supportive care is also a comparator for idelalisib

3.3 The clinical experts stated that, at third line, most people would currently be offered chemotherapy, but those who could not have chemotherapy would be offered best supportive care instead. The clinical experts stated that some of those people could take idelalisib because it has a different toxicity profile to chemotherapy. So, while people may not tolerate the specific adverse effects of chemotherapy, they may tolerate those of idelalisib. The committee concluded that best supportive care is an option for people who cannot have chemotherapy.

Stem cell transplantation is used at second and subsequent lines

3.4 The clinical experts stated that response to second-line treatment is consolidated with autologous stem cell transplantation in people who are considered fit enough, in line with NICE's guideline on [non-Hodgkin's lymphoma: diagnosis and management](#). They also noted that autologous stem cell transplantation may be offered at later lines of therapy in people whose disease responded well to treatment. The clinical experts considered stem cell transplantation to be an important prognostic factor and that it could be used after idelalisib. The committee concluded that it

was possible for idelalisib to be used as a bridge to stem cell transplantation, if there was a sufficient response to idelalisib.

Clinical evidence

The key clinical evidence comes from the DELTA study

3.5 The key clinical evidence for idelalisib came from the single-arm phase II DELTA study, which included 125 patients with indolent (slowly growing) non-Hodgkin's lymphoma, 72 of whom had follicular lymphoma refractory to 2 or more lines of treatment. The primary outcome measure was overall response rate. Overall survival and progression-free survival were among the secondary outcomes. Median progression-free survival was 11.0 months; median overall survival was not reached, but the company estimated it at 38.1 months. The company supplemented the DELTA study with 2 other sources of evidence for both idelalisib and the comparators:

- A Compassionate Use Programme (CUP): retrospective observational data from patients with follicular lymphoma treated compassionately in the UK and Ireland. The company took a subset of 79 patients who had relapsed or refractory follicular lymphoma and who were given idelalisib. In these patients, median progression-free survival was 7.1 months, and median overall survival was not reached.
- The UK Haematological Malignancy Research Network (HMRN) registry: retrospective observational data from 26 patients with follicular lymphoma refractory to 2 previous lines of therapy including rituximab and chemotherapy at first or second line who had chemotherapy at third line. Median progression-free survival was estimated at about 17 months, median overall survival was reported as 20 months.

It is unclear whether the DELTA population or the CUP cohort more closely reflects clinical practice

3.6 The committee discussed the generalisability of the 2 study populations to the decision problem:

- It questioned why only 79% (and not 100%) of patients in DELTA had disease refractory to 2 or more lines of therapy. The company explained that some patients had had an anti-CD20 monoclonal antibody and an alkylating agent together in the same line of therapy (rather than sequentially), which the company defined as a single treatment regimen.
- It noted the difference in Eastern Cooperative Oncology Group (ECOG) performance status and FLIPI scores between DELTA and the CUP. Notably, 8.3% of patients in DELTA had an ECOG score of 2–4 compared with 25.0% of patients in the CUP, reflecting poorer performance among patients in the CUP. The clinical experts stated the ECOG performance status in CUP more closely reflected clinical practice than that in DELTA.
- The clinical experts noted that the time since completing the last therapy was shorter in DELTA than in the CUP, suggesting that patients in DELTA had poorer prognosis.

Although the committee agreed that the populations in DELTA and the CUP were different, it was difficult to assess the degree of heterogeneity between them. The studies differed in design (for example, how they defined disease progression). Also, patient and disease characteristics at baseline differed, with some suggesting a more favourable prognosis in DELTA than in the CUP and others suggesting the contrary. The company argued that the population enrolled into DELTA better reflected clinical practice. The clinical experts, however, suggested that the CUP cohort was more likely to reflect the intended UK treatment population because it was a ‘real-

world' study, although they acknowledged that such studies lack the methodological rigour typical of a clinical trial. The committee concluded that it would consider both studies in its decision-making.

Indirect treatment comparisons

'Self-control' comparisons with previous lines of therapy do not give reliable comparator information

3.7 In the absence of a head-to-head randomised comparison of idelalisib with chemotherapy, the company compared progression and death on idelalisib with the last line of chemotherapy before idelalisib, for each study. Therefore, the company used the previous line of chemotherapy as a proxy for chemotherapy at the next line of treatment (that is, the point at which idelalisib would be used). It got these data from DELTA and the CUP. The committee discussed several issues around this:

- The ERG commented that this comparison should be considered with caution because of the bias from including only those patients who survived to have idelalisib. These patients would have been healthier than the entire chemotherapy-receiving population that existed at the previous line, including those who died and so could not have idelalisib. The committee agreed that this was a source of selection bias in favour of idelalisib.
- The committee recognised that patient fitness and treatment effectiveness could decline between 1 treatment line and the next. Therefore, comparing idelalisib with the previously received chemotherapy was not comparing like with like, and could have introduced bias against idelalisib.
- For DELTA, the previous line of therapy data was based on 'clinician recall' (because people entered the study at the point at which they would have idelalisib), which may be subject to recall bias. The committee was aware that the definition of trial-based and historical progression may differ, and that progression was more likely to be

identified more quickly during a clinical trial when patients are actively monitored. The committee recognised this would bias against idelalisib.

- The clinical experts recognised that it was difficult to draw conclusions on the comparative effect of idelalisib by looking retrospectively at previous lines of therapy, and more so in the CUP. This was because time to progression on idelalisib was already determined retrospectively, and treatment previous to that was even more in the distant past.
- For both trials, previous lines of therapy reflected a range of chemotherapy regimens, at a range of different points in the treatment pathway (from third to fourteenth line). These regimens may differ from one another in clinical effectiveness and adverse effects, and may not represent patients whose condition is at the third-line 'double-refractory' stage.
- The committee noted that DELTA began recruiting patients whose condition was at the 'double-refractory' stage in 2011 from a range of countries. It recognised that chemotherapy options available for previous treatment in DELTA may have changed over time and may have differed in other countries. Therefore, the chemotherapy treatments used may not represent current UK clinical practice.

The committee recognised that this 'self-control' comparison did not compare the same patients with each other because the company had not done a paired matched analysis. Instead, it compared one population (having chemotherapy) with itself after patients had progressed and survived to have another treatment (having idelalisib). It concluded that there were multiple sources of bias in this type of analysis, and that the overall direction of bias and effect on relative effectiveness could not be determined.

The results from DELTA and the CUP are inconsistent

- 3.8 The committee noted that comparing idelalisib with previous chemotherapy gave inconsistent results in DELTA and the CUP. The

results from DELTA suggested an increase in progression-free survival compared with last previous therapy, whereas the results from the CUP showed similar progression-free survival compared with last previous therapy. The clinical experts commented that this might be because of how progression was determined and how relapse was identified, given the indolent nature of the disease. They also noted that the CUP, being a 'real-world' study, was likely to have defined and assessed disease progression more loosely than DELTA. The committee agreed that, although this approach addressed the issue of defining standard of care, (see section 3.2), the results were associated with a high degree of bias and did not give reliable comparator information.

The matching adjusted indirect comparison with the HMRN gives an estimation of the effect of chemotherapy in the DELTA study population

3.9 In addition to the 'self-control' comparison, the company presented an unanchored matching adjusted indirect comparison (MAIC) with the HMRN cohort (see section 3.5). The company matched individual patient-level data from the HMRN cohort to the population-level descriptive characteristics of patients in the DELTA study. This estimated the effects of chemotherapy in the DELTA population. The ERG preferred estimating the effect of idelalisib in the HMRN (UK) population because this gave a larger source of individual patient data and a more robust dataset to the adjustments done in the MAIC. The committee agreed that there was merit in matching the DELTA population to the HMRN cohort to explore uncertainty and give a better representation of clinical practice. It also considered that, because patient-level data were available from both DELTA and the HMRN cohort, the company could develop a propensity score. The committee also recognised that without sufficient information on potential confounders, this method could be biased.

The MAIC does not adjust appropriately for potential confounders

3.10 The committee discussed what factors most affect prognosis and therefore should have been included in the MAIC analysis. The committee

was aware it had not been presented with a systematic review of risk factors for progression and death to inform the MAIC. In addition to history of autologous stem cell transplantation (see section 3.4), the committee understood that there are other factors associated with progression and death. These include, but are not limited to, the components of the Follicular Lymphoma International Prognostic Index I and II (FLIPI and FLIPI2), notably age, serum beta 2 microglobulin levels, bone marrow involvement, size of the largest involved lymph node, and haemoglobin levels. Other factors include time in previous remission, time since completing the last therapy, comorbid conditions, and which chemotherapeutic agents the patient has had previously. The clinical experts suggested that the FLIPI index is the best validated prognostic tool, but that it is has limited value at third line. They proposed that a key prognostic indicator would be response to previous therapy, but this input was not captured in the variables chosen in the MAIC. The company matched 5 of 7 variables that it assumed accounted for all prognostic factors and treatment-effect modifiers. The committee was aware that a technical support document published by the Decision Support Unit recommends that, when only single-arm trial data are available, all the characteristics that could influence the outcomes of interest should be adjusted. However, increasing the number of matched characteristics reduced the effective sample size and hence the precision of the estimates. For example, when the company removed the variable 'median time since diagnosis' from the adjustment, estimated 2-year overall survival reduced by more than 20%. The committee also appreciated that, in any case, there would be unobserved differences between study populations that would not be accounted for. It noted that this would bias the estimates of relative effectiveness if associated with progression or death. The ERG commented that the MAIC should be treated with caution because the equivalent sample size was very small (n=6.9), the adjustment was very sensitive to variable selection and there was no sensitivity analysis done despite these uncertainties. The committee

concluded that, based on the company's MAIC, it could not ascertain whether the estimated effect of idelalisib compared with chemotherapy reflected what would be seen in clinical practice.

The 'blended' comparator assumes that different chemotherapeutic treatments are similarly effective but this assumption is not justified

3.11 The committee was aware that the NICE scope listed the chemotherapeutic agents separately, and had heard from clinical experts that the therapies are likely to differ in effectiveness and tolerability. It recognised that the company had combined treatments together, which reflected a 'blended' comparator, and which NICE's [guide to the methods of technology appraisal](#) discourages. The committee considered that evidence for the effectiveness of separate chemotherapeutic agents might exist from the trials that provided the evidence for the use of chemotherapy, or from registries other than the HMRN, but also considered that the evidence may be difficult to source. The committee concluded that it had not been presented with evidence that justified the assumption that chemotherapeutic agents could be considered similarly effective to one another and in line with current UK practice.

There are no data for best supportive care

3.12 The committee recognised that the company did not provide a source of data to describe the natural history of disease in patients having best supportive care. The committee asked the company whether the HMRN cohort could provide this, or whether clinical trial data were available from control arms of clinical trials of chemotherapy. The committee concluded that the company had not explored this, but that this would be needed to make a comparison with best supportive care.

The current analyses do not represent a reliable source of comparator information

3.13 The committee considered that there was high degree of clinical uncertainty in the evidence base because the company had not provided

direct comparative evidence and the 2 analyses comparing idelalisib with standard of care were not suitable for decision-making. The committee queried the company at the meeting as to whether other observational data for idelalisib exists globally, and understood that such data might exist from CUPs in other countries. The committee discussed how the evidence could be improved by:

- considering better (larger, better characterised) populations from other registries and updated data from the HMRN registry
- redoing the analyses using the DELTA population as the source of individual patient data, which would increase the effective sample size and give less weight to individual patient data (see section 3.9)
- validating the MAIC against another dataset (the CUP cohort or international data) to prove a similar magnitude of the effect estimate and changes in it from adjustment, that is, estimating the effect of idelalisib in the other cohort (for example, the CUP cohort) and comparing that estimate with the observed effect of idelalisib in the cohort
- doing a sensitivity analysis on the number of matched characteristics (see section 3.10)
- carrying out propensity-score matching as an alternative to the matching adjustment, considering the availability of both individual patient datasets
- considering evidence from treatment arms of clinical trials used to establish the effectiveness of chemotherapy (see section 3.12).

The company's economic models

The model structures are appropriate for modelling

3.14 The company presented 4 economic analyses using different model structures and sources of clinical data, which are summarised in table 1.

Table 1 Summary of comparisons used in the economic modelling

Comparison	Idelalisib data source	Comparator data source	Model type
A (company base case)	DELTA	Chemotherapy: DELTA data from 'self-control' previous line of treatment as a proxy for current chemotherapy	Markov cohort – state transition
B	DELTA	Chemotherapy: Matching adjusted survival data from chemotherapy regimens of the HMRN cohort	Partitioned survival model
C	Data from the CUP cohort and DELTA	Chemotherapy: Time-to-progression data from 'self-control' previous line of treatment as a proxy for current chemotherapy	Markov cohort – state transition
D	DELTA	Best supportive care: No treatment costs because company assumes instant disease progression	Markov cohort – state transition

Abbreviation: HMRN, Haematological Malignancy Research Network.

Comparisons A, C and D reflected state transition models in which the movements between states (clinical events) are governed by 'transition probabilities', and expected costs and quality-adjusted life years (QALYs) are estimated by assigning values to the time spent by patients in each state. Comparison B used the more conventional 'partitioned survival analysis' approach in which the proportion of patients in each state at each time point is determined from a set of survival curves, rather than transition probabilities. For this approach, an overall survival curve is needed to estimate the proportion of people alive over time directly. This was not available in comparisons A and C because the comparator data came from the 'self-control' comparisons that, by definition, excluded patients who had died. The committee concluded that it was important to bear in mind the different modelling approaches used when comparing the resulting cost-effectiveness estimates.

One key area of uncertainty in the economic models is how previous line chemotherapy effectiveness was adjusted using a 'hazard ratio'

3.15 In comparisons A and C, which used 'self-control' data, the company applied a 'hazard ratio' to adjust for the expected decline in the

effectiveness of chemotherapy later in the treatment pathway (see section 3.7). Specifically, it estimated that effect declines by 25%. The ERG commented that it could not verify the data source underpinning this assumption. The committee recalled that a range of chemotherapy regimens was being used and these varied in effectiveness (see section 3.1). This meant that applying a single estimate reflecting the decrease in treatment effect across the whole range of regimens was unlikely to be reliable. Furthermore, the hazard ratio adjustment affected the cost-effectiveness estimate for comparison C to a much greater extent than comparison A, and the committee questioned why this was the case. The ERG commented that, when comparing progression-free survival for those having idelalisib against an unadjusted previous line of therapy, DELTA had a much greater difference than the CUP. Therefore, the addition of a hazard ratio had a greater effect on the CUP cost-effectiveness estimates. The committee concluded that using the hazard ratio introduced additional uncertainty to the model that needs to be explored in sensitivity analyses.

The different modelling structures influence which clinical inputs drive the modelled survival differences and therefore the cost effectiveness

3.16 The committee agreed that it would focus on comparisons A (company's base case) and B. It was not presented with a clear rationale for using both DELTA and CUP sources of data without adjustment for using different populations to inform the clinical inputs of comparison C. It noted that the company did not provide best supportive care data for comparison D (see section 3.12). However, it agreed that it could use comparisons C and D to evaluate its preferred analyses:

- In comparison A, the company modelled survival in the Markov model from pre-progression and post-progression states. The pre-progression state assumed transition to death at a rate of 5.71 times the age- and sex-adjusted general population. Post-progression survival was modelled on an exponential fit of observed post-progression survival in

the DELTA population. Mortality was greater in the post-progression state so the time to progression was the most important transition in the Markov model. Therefore, the model was most sensitive to the time-to-progression transition.

- In comparison B, the company modelled survival based on extrapolating survival data between DELTA and the adjusted HMRN dataset using partitioned survival analysis. Overall survival conferred a higher utility increase than progression in this model, so the key driver in survival difference between idelalisib and chemotherapy was the comparison of overall survival. The company used the overall survival data that it had adjusted using the MAIC (see section 3.9). Therefore, the model was most sensitive to the overall survival estimations.

The model estimates of survival are uncertain

3.17 The committee considered the survival estimates produced by the different comparisons:

- Comparisons A, C and D consistently predicted longer overall survival for idelalisib than comparison B at all observed time points. The company and the ERG gave alternative explanations for this, which both drew on the different modelling approaches used (see section 3.14). The company indicated that, in comparisons A and C, overall survival for idelalisib (modelled indirectly) was driven by post-progression survival, and this was less mature than the overall survival data used in comparison B. The ERG commented that a potential reason for the discrepancy was that time to progression and post-progression survival are likely to be correlated, but the company in its model assumed that these 2 transitions are independent. However, the ERG was unable to check this reasoning without access to the individual patient data. In general, the committee agreed that comparison B seemed to fit the observed overall survival data for idelalisib better than the other comparisons.

- For comparison A, the committee noted that the model was sensitive to the choice of the distribution to fit the observed idelalisib time-to-progression data in DELTA. Both log-normal and exponential curve extrapolations of observed time to progression offered a plausible fit within the time limits of the observed trial but differed greatly over the 38-year time horizon. The log-normal fit gave greater weight in the model to a small number of patients in whom disease did not progress within 10 years, which the committee agreed seemed implausible. Furthermore, the committee heard from the clinical experts that, at this stage of the disease, the life expectancy of people having chemotherapy is expected to be less than 2 years. However, the model predicted a significantly greater mean life expectancy of around 5 years in the chemotherapy arm.
- For comparison B, the committee noted an implausibly large difference in survival at 1 year between idelalisib and chemotherapy. This was confirmed by clinical experts, who advised that the model was likely to have overestimated the difference in short-term overall survival between idelalisib and chemotherapy, but that the differences appeared more reasonable in the longer term.

The committee agreed that the survival modelling reflected a high degree of uncertainty in the evidence. Given the lack of direct comparator data, the absence of evidence for individual chemotherapeutic regimens or for best supportive care, and the paucity and immaturity of observed data, the committee considered that it was important that the survival estimates aligned as closely as possible with whatever data were observed. In the current analyses, the Markov model (comparisons A, C and D) consistently overestimated the effect of idelalisib and the approach (B) using partitioned survival analysis appeared to have markedly underestimated the effect of chemotherapy. Therefore, the committee concluded that the model predictions were not reliable for decision-making.

The ‘blended comparator’ masks ineffective treatments

- 3.18 The committee considered that using a blend of chemotherapeutic regimens as a comparator meant averaging the cost effectiveness of the treatments included, and potentially masked cost-ineffective individual treatments. The committee concluded that the cost effectiveness of idelalisib therefore needed to be considered against each chemotherapy treatment individually.

Utility values in the economic models**Utility values based on the DELTA study should be explored**

- 3.19 The company presented utility values to reflect health-related quality of life from a published study and the ERG presented scenario analyses with alternative utility values from other published studies. The clinical experts agreed that all values seemed reasonable because people with follicular lymphoma can expect a high utility value once the bulk of the disease has decreased. The ERG questioned why the company did not use health-related quality-of-life data (FACT-G instrument) from DELTA. The company responded that there were no mapping algorithms available for the target population and that the FACT-G instrument does not capture key elements of quality of life in patients with follicular lymphoma. The committee concluded that, nevertheless, this analysis would be useful as validation of the chosen utility inputs.

Adverse effects with idelalisib are different than those with chemotherapy

- 3.20 The committee noted the potential serious adverse effects in people having idelalisib outlined in the European Medicine Agency’s Risk Management plan, which include severe drug-related colitis, pneumonitis and organising pneumonia, and serious infections. The company did not provide relative safety data for chemotherapy. The clinical experts commented that adverse events with chemotherapy are qualitatively different to those with idelalisib, so it is difficult to comment on the comparative safety profiles. The committee considered that the adverse

effects of chemotherapy are unlikely to differ between haematological malignancies. The company included adverse events as disutilities within all the economic models, these disutility values were based on various sources and the incidence was estimated using data from DELTA. The company models assumed the same incidence of disutilities for both idelalisib and chemotherapy. The clinical experts commented that idelalisib and chemotherapies will all have different toxicities, but idelalisib has generally been well tolerated within its risk management plan. The committee noted that adverse event disutility is not a key driver in the model. It concluded that idelalisib is unlikely to have the same adverse event disutility as the average disutility for possible chemotherapy treatments, but is unlikely to markedly change the outcomes from the model.

Cost-effectiveness estimates

There are no plausible cost-effectiveness estimates

3.21 The company presented a base-case incremental cost-effectiveness ratio (ICER) for comparison A of £26,076 per QALY gained. However, this increased to £32,882 per QALY gained with the ERG's corrections to the model. The company also presented an ICER of £47,011 per QALY gained for comparison C, which increased to £58,754 per QALY gained with the ERG's corrections. Because of the substantial uncertainty around the clinical and cost inputs to the model, the committee considered that none of these estimates were valid. Furthermore, all ICERs presented were deterministic, which does not reflect the uncertainty in the evidence base. The committee also recognised, in line with NICE's [guide to the methods of technology appraisal](#), that given the high level of uncertainty associated with the analyses it would be inappropriate to consider idelalisib to be a cost-effective use of NHS resources unless the most plausible ICER values were towards the lower end of the maximum acceptable ICER range (that is, £20,000 per QALY gained). The committee concluded that none of the ICERs presented, which ranged

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between £16,855 and £95,120 per QALY gained, were reliable or accurate estimates, so idelalisib could not be considered cost effective.

The current analyses do not represent a reliable source of cost effectiveness but could be improved

3.22 The committee agreed that the key uncertainties in the model came from the modelling of survival outcomes, namely:

- use of the hazard ratio estimate to adjust previous lines of treatment in comparisons A and C (see section 3.15)
- inconsistency of model survival outputs between comparisons A and B (see section 3.17)
- time-to-progression extrapolation in comparisons A and C (see section 3.16)
- reliability of overall survival curves used in comparison B (see section 3.17)

To improve the quality of the evidence and further characterise the uncertainty, the committee agreed that additional analyses around the key model parameters should be presented. These could include:

- calibrating the Markov models for comparisons A, C and D to better match model predictions of the observed data
- carrying out alternative MAIC adjustment scenarios from the sensitivity analysis of the MAIC adjustment, including number of matched characteristics and population in which the adjustment took place
- exploring uncertainty around the cost effectiveness of individual chemotherapy regimens
- doing a probabilistic sensitivity analysis for all comparisons to capture the uncertainty within each ICER estimate.
- exploring trial-based utility values in all comparisons (see section 3.19).

End of life

The committee concluded there was not enough information about end-of-life considerations

3.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [guide to the methods of technology appraisal](#):

- The committee discussed whether the mean life expectancy using standard care was likely to be less than 24 months. It was presented with a median life expectancy from the 26 patients in the HMRN cohort and a mean life expectancy as modelled in comparison A, which was considerably greater. The committee noted the large difference between the estimates, which highlighted concerns around the data modelling. It concluded that the median overall survival from the HMRN cohort was the most relevant, but likely underestimated the mean life expectancy. However, the committee raised concerns about the limited number of patients and the selection of only patients who had chemotherapy as third-line treatment. The committee concluded that the evidence for short life expectancy was not robust and more evidence was needed.
- Given its concerns about the modelling and the inputs to the model, the committee did not consider that the model generated a valid estimate of the mean extension to life given by idelalisib. The committee concluded that the information presented was not robust enough to conclude that idelalisib is a life-extending treatment.

Cancer Drugs Fund

Idelalisib is not a candidate for the Cancer Drugs Fund

3.24 Having concluded that idelalisib could not be recommended for routine use, the committee then considered whether it could be recommended for treating follicular lymphoma within the Cancer Drugs Fund. The committee

discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's [Cancer Drugs Fund methods guide \(addendum\)](#). It also noted that the company had not expressed an interest in providing idelalisib through the Cancer Drugs Fund. The company confirmed that there are no ongoing comparative trials that will be able to provide more robust, controlled evidence. The committee appreciated that the Cancer Drugs Fund is designed to resolve uncertainties, and that the key uncertainty in this appraisal were the assumptions surrounding the effectiveness and adverse effects associated with chemotherapy. It was aware that the Cancer Drugs Fund could collect data on the intervention (idelalisib), but not the comparator (chemotherapy), so would not be able to resolve this uncertainty. Also, the committee could not determine whether idelalisib had 'plausible potential' to be cost effective (see section 3.21). It concluded that idelalisib could not be recommended for use within the Cancer Drugs Fund as an option for follicular lymphoma that had not responded to 2 previous lines of therapy in adults.

Innovation

It is not clear if idelalisib is innovative

3.25 The committee noted that idelalisib is innovative in that it has a different mechanism of action to other available treatments for 'double-refractory' follicular lymphoma, and addresses an area of unmet clinical need (see section 3.1). It concluded that the model captured all quality-of-life improvements, including its oral route of administration. However, the committee could not determine whether it reflected a step change in treatment, given the uncertain estimates of comparative effectiveness.

Conclusion

Idelalisib is not recommended

3.26 The committee was not presented with enough reliable information to be able to address the decision problem. Therefore, it could not recommend idelalisib for the routine treatment of follicular lymphoma that has not responded to 2 previous lines of treatment in adults.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
September 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Technical Lead

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Technical Adviser

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