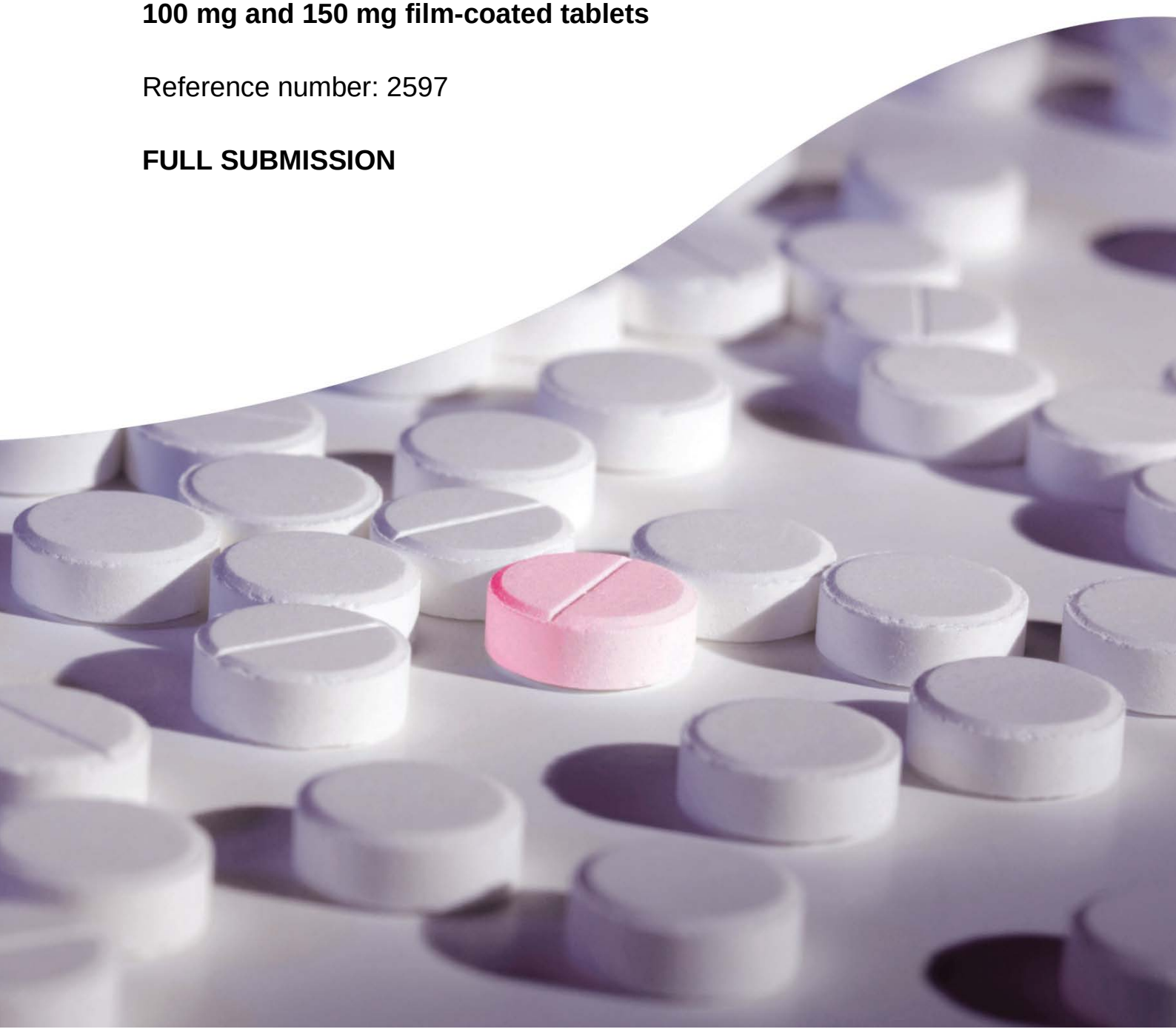
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Idelalisib (Zydelig®)
100 mg and 150 mg film-coated tablets

Reference number: 2597

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Idelalisib (Zydelig®▼) 100 mg and 150 mg film-coated tablets

This assessment report is based on evidence submitted by Gilead Sciences Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Idelalisib (Zydelig®▼) as monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	The recommended dose of idelalisib is 150 mg taken orally, twice daily, with or without food. Treatment should be continued until disease progression or unacceptable toxicity[2]. Refer to the SPC for further information on dosing, special warnings and precautions for safe use[2].
Marketing authorisation date	19 September 2014

2.0 DECISION CONTEXT

2.1 Background

Follicular lymphoma is the most common form of low-grade non-Hodgkin's lymphoma, a cancer that affects the lymphocytes[3]. It develops slowly and often without symptoms, over many years[4]. The most likely symptom is painless, swollen lymph nodes in the neck, armpit or groin[4]. Follicular lymphoma is more common in people aged over 50 and over 70% of cases are diagnosed in people aged over 60 years[3,4].

Follicular lymphoma is characterised by a relapsing-remitting disease course, over several years; with successive responses to treatment becoming harder to achieve and lasting for shorter periods[4]. Advanced stage III to IV lymphomas will eventually become resistant to treatment and transform to high-grade or aggressive lymphomas[4].

Treating follicular lymphoma focuses on increasing life expectancy and increasing health-related quality of life[4,5]. The National Institute for Health and Care Excellence (NICE) treatment pathway recommends rituximab as first-line treatment for people without symptoms and rituximab plus chemotherapy for people with symptoms[4,6]. Choice of salvage treatment after relapse depends on the efficacy of previous treatment regimens[7] and recommendations for treating advanced-stage relapsed or refractory follicular lymphoma include rituximab in combination with chemotherapy or rituximab monotherapy if all other treatment options have been exhausted[6]. Autologous or allogeneic stem cell transplantation may be considered for people in second or subsequent remission if they are fit enough[6]. People for whom further rituximab or chemotherapy is inappropriate may receive best supportive care[1].

Idelalisib is the first of a new class of inhibitors of phosphatidylinositol 3-kinase (PI3K) p110delta, a protein that is hyperactive in B-cell cancers and is central to multiple signalling pathways of malignant cells in lymphoid tissues and bone marrow[2].

2.2 Comparators

The comparator included in the company's submission for the economic analysis was a mix of chemotherapy-based regimens based on previous treatments received by patients in a pivotal study. These included:

- rituximab plus CHOP(cyclophosphamide, doxorubicin, vincristine, prednisolone)
- rituximab (MabThera®)
- rituximab plus bendamustine
- rituximab plus CVP (cyclophosphamide, vincristine, prednisolone)
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)
- rituximab plus prednisolone
- rituximab plus CHO (cyclophosphamide, doxorubicin, vincristine)
- CVP (cyclophosphamide, vincristine, prednisolone)
- rituximab plus fludarabine
- CHPE (cyclophosphamide, doxorubicin, prednisone, etoposide)
- rituximab plus chlorambucil
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- CHEPi (cyclophosphamide, doxorubicin, etoposide, prednisone, interferon)
- chlorambucil plus prednisolone
- fludarabine plus mitoxantrone[1].

2.3 Guidance and related advice

- NICE Guideline NG52 (2016) Non-Hodgkin's lymphoma: diagnosis and management[8]
- NICE Technology Appraisal TA359 (2015) Idelalisib for treating chronic lymphocytic leukaemia[9]
- European Society for Medical Oncology (2014) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of newly diagnosed and relapsed follicular lymphoma[7]
- South Wales Cancer Network (2013) Follicular lymphoma haematological pathway[10]
- NICE Technology Appraisal TA243 (2012) Rituximab for the first-line treatment of stage III-IV follicular lymphoma[4]
- British Committee for Standards in Haematology (2011) Guidelines on the investigation and management of follicular lymphoma[5]
- NICE Technology Appraisal TA137 (2008) Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma[11]

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of subcutaneous rituximab (MabThera®) in combination with chemotherapy to treat stage III to IV follicular lymphoma that has not previously been treated, and as maintenance therapy for follicular lymphoma that responds to induction therapy[12].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes data from a single arm phase II study (study 101-09) of the efficacy and safety of idelalisib in 125 people with relapsed indolent non-Hodgkin's lymphoma and post-hoc analyses of data from 72 people in the study who had follicular lymphoma[1]. Two phase I studies that included people with indolent non-Hodgkin's lymphoma were also included in the submission but will not be discussed in detail here.

3.1 Study 101-09

This open-label study was conducted in the USA and Europe and enrolled 125 patients (aged > 18 years) with confirmed B-cell indolent non-Hodgkin's lymphoma without evidence of transformation who had received at least two previous treatments[13]. Patients were enrolled if they had a Karnofsky performance score of 60 or higher (defined as patients needing occasional assistance but able to care for most of their personal needs; ECOG grade 2), and their disease was refractory to treatment with rituximab and an alkylating agent (defined as less than a partial response or progression of disease within 6 months after completing previous therapy).

Most patients (89%) had stage III or IV disease and 72 (58%) had follicular lymphoma grade 1, 2 or 3a. The median age of patients was 64 years (range 33–87 years). All patients were given oral idelalisib at a dose of 150 mg twice daily, until progression of disease, unacceptable toxic effects or death[13].

The primary endpoint was overall rate of response: complete response and partial response were assessed using standard criteria for lymphoma by an independent review committee[13]. Secondary efficacy endpoints included time to a response, duration of a response, progression-free survival and overall survival. Results for the primary and secondary endpoints are shown in Table 1.

Table 1. Clinical response outcomes from study 101–09 (at data cut-off June 2014, 20 months after last patient enrolment)[13-16]

Independent review committee assessment: ITT analysis	Total population (n = 125)	Follicular lymphoma population (n = 72)
Primary endpoint		
Overall response rate, n (%) (95% CI)	72 (58%) (48.4 to 66.4)	40 (56%) (43.4 to 67.3)
- complete response	12 (10%)	10 (14%)
- partial response	59 (47%)	30 (42%)
Secondary endpoints		
Median time to a response	1.9 months* (95% CI: 1.8 to 3.7)	2.6 months (range, 1.6 to 11.0)
Median duration of response (95% CI)	12.5 months (7.4 to 26.9)	11.8 months (6.4 to 26.9)
Median progression-free survival (95% CI)	11.0 months (8.3 to 13.8)	11.0 months (0 to 30.6)
Median overall survival (95% CI)	30.8 months (26.8 to not reached)	Not reached
* At data cut-off June 2013 (8 months after last patient enrolment) CI: confidence interval; ITT: intent-to-treat		

At the data cut-off of June 2013 110 patients (90% of the total population) had a reduction in the size of lymph nodes during treatment[13]. At the June 2014 data cut-off, the response rates were similar between the total population and the follicular lymphoma population: 58% and 56%, respectively[15,16]. For the 72 patients in the subgroup with follicular lymphoma median progression-free survival was 11 months, whereas that associated with the previous line of treatment on entering the study was 5.1 months (range 4.4 to 6.0 months)[16]. Within the follicular lymphoma subgroup the median Kaplan–Meier estimated overall survival was not reached in 20 months of follow-up after the last patient was enrolled; in this group the estimated overall survival at 24 months was 69.8%[16].

Health-related quality of life data collected using the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) questionnaire, showed that health-related quality of life improved or was stable[16]. The median best change from baseline in FACT-Lym score showed clinically meaningful improvement at least once during follow-up for the subscales of emotional well-being, functional well-being, additional concerns, trial outcome index score and FACT General total score subscales[16].

3.2 Comparative safety

In the total population for study 101-09, 123 patients (98.4%) reported at least one adverse event and 90 patients (72%) reported at least one serious adverse event[17]. In the follicular lymphoma subpopulation 71 patients (98.6%) reported at least one adverse event and 47 (65.3%) reported at least one serious adverse event[17].

Of all grade treatment-emergent adverse events reported in 10% or more of the population, neutropenia (19.4%), diarrhoea (13.9%) and pneumonia (6.9%) were the most common grade 3 or above treatment-emergent adverse events reported in the follicular lymphoma subpopulation[17].

For the whole population the most common treatment-emergent adverse event in study 101-09 was diarrhoea, reported in 54 patients (43%), of whom 16 (13%) had grade 3 or higher; these were managed with interruptions in treatment or dose adjustments[13].

In March 2016, three phase III studies evaluating idelalisib were stopped because of a high rate of serious adverse events and deaths[18]. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a safety review of idelalisib, after which the Committee for Medicinal Products for Human Use (CHMP) confirmed that the benefits of idelalisib for treating chronic lymphocytic leukaemia and follicular lymphoma outweighed the risk of side effects[19]. The three studies had used idelalisib in unlicensed combinations with other medicines or in patient groups for whom it is not licensed. A review was undertaken by PRAC and to minimise the risk of serious infections CHMP recommended extra measures such as extra monitoring requirements and antibiotic prophylaxis[19]; the SPC was updated accordingly[2].

3.3 AWTTC critique

- NICE guidelines for advanced stage relapsed or refractory disease recommend rituximab in combination with chemotherapy, rituximab monotherapy as maintenance therapy or rituximab monotherapy when all alternative treatment options have been exhausted. Guidelines suggest that the choice of treatment for relapsed disease depends on factors such as previous treatment regimens, duration of response and a patient's fitness for therapy[4,8,10,11]. Treatment pathways for double-refractory follicular lymphoma are not well defined and there is no standard of care.
- Study 101-09 provided no comparative clinical efficacy data and was conducted in a broader patient population than the indication under consideration. Although most patients (72 of 125; 57.6%) had follicular lymphoma that was refractory to two previous treatments, the study does not appear to have been designed to evaluate idelalisib in treating follicular lymphoma. Data are provided from post-hoc analyses conducted in this small subpopulation.
- Study 101-09 was open-label and there was no comparator arm, however, CHMP recognises that because the size of the population with double-refractory lymphoma is small, and there is no single standard treatment option, it would not be ethical or feasible to conduct a randomised comparative study[20]. The primary endpoint was overall response, which is an acceptable endpoint in single-arm studies[21]. All responses and disease progression were evaluated by an independent review committee[13]. Overall survival was not a primary endpoint, although designing a clinical study adequately powered to measure overall survival would need a large number of patients, and may not be feasible[20].
- A clinical expert consulted by the company stated that, in Wales, 70–80% of people with follicular lymphoma would be treated with rituximab plus CVP and 10–20% with rituximab plus CHOP, and that rituximab monotherapy is not used[22]. However, the company's survey was conducted before NICE published its guideline for non-Hodgkin's lymphoma in July 2016.

- The latest data cut-off for study 101-09 is June 2014, when the median overall survival for patients with follicular lymphoma had not been reached and overall survival was only estimated at 69.8% at 24 months[16].
- There are significant safety concerns associated with taking idelalisib, although the CHMP's safety review, conducted in 2016, confirmed that the benefits of idelalisib treatment outweigh the risks of side effects[19]. The SPC has been updated with the CHMP's safety recommendations for people taking idelalisib, which include: antibiotic prophylaxis to prevent *Pneumocystis jirovecii* pneumonia, regular blood tests to monitor for neutropenia and monitoring for signs and symptoms of infection[2,18]. In addition, idelalisib has a positive NICE recommendation for chronic lymphocytic leukaemia within its licensed indication and AWTTC-sought clinical expert opinion confirms that clinicians in Wales have experience in using this medicine in chronic lymphocytic leukaemia and therefore would be familiar with managing this treatment, including adverse events.
- Idelalisib is available as an oral formualtion[2], which may be an advantage over rituximab formulations and/or chemotherapy[23,24].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost utility analysis comparing the oral administration of idelalisib 150 mg twice daily with the current standard of care, in treating people with follicular lymphoma who are refractory to two previous lines of treatment. It is assumed that standard care is similar to what is received at previous line by patients in study 101-09[13] (see section 2.2 for list of comparators), in those people for whom chemotherapy is suitable. For people for whom chemotherapy is not appropriate best supportive care is the chosen comparator.

The cost utility analysis takes the form of a five-state *de-novo* Markov model, with one-week cycles and a 15-year time horizon. The model adopts an NHS/Personal Social Services perspective and assumes that all patients start in the 'pre-progression on treatment' state. Patients can remain in this state or transition to the 'pre-progression off treatment', 'post-progression' or 'palliative care' states. It is possible to transition to the 'death' state from any of the disease-related health states via the transitory 'palliative care' state. Pre-progression mortality is assumed to be equal to the general population rate, calculated from Office for National Statistics life tables for Wales[25]. This model structure has been validated by one company-sought clinical haematologist in Wales.

Post-progression survival, time to progression (TTP) and time on treatment (ToT) are informed by follicular lymphoma subgroup data extracted from study 101-09, a pivotal phase II, open-label, single-arm study of idelalisib[13] (see section 3.1). Notably, the data from this study lack maturity: over 60% of patients remained in the sample at the end of the data collection time period. Observed data were therefore fitted to a variety of common parametric distributions to predict longer term outcomes. TTP and post-progression survival have been used to model patient survival. Given the data limitations of the study, it is assumed that post-progression survival is equal across model arms. The company proposes that this may underestimate the survival benefit of idelalisib, given that previous research suggests a positive relationship between progression-free survival and overall survival in advanced cancer[26]. The distributions used for extrapolation have been assessed in terms of goodness of fit using standard statistical tests. Choice of distribution has been guided by visual inspection by a company-sought expert haematologist in Wales. Although the statistical tests suggest that the Gompertz curve fits best with the post-progression survival Kaplan–Meier data, the exponential curve has been used for the base case, given that this distribution

predicts that only a small proportion of patients survive in the long term. Similarly, despite the gamma model having the best statistical fit for TTP data, the exponential distribution has been used in the base case following clinical expert advice. ToT has also been extrapolated; the generalised gamma distribution revealed the best statistical fit and was considered the most appropriate by a clinical expert.

No utility data were collected in study 101-09. A systematic literature search conducted by the company identified just one relevant study[27], which assessed health-related quality of life in 222 adults with follicular lymphoma in the UK. This study has informed several previous economic evaluations[28-30], and collected EQ-5D utility scores for progression-free (0.805) and progressed disease (0.618) states. These values have undergone clinical review and are considered to reflect the detriment associated with disease progression. However, they are regarded to be too high for people whose disease is double refractory. Utility decrements have been included in the model to reflect the impact of grade 3 and 4 adverse events. These decrements have been informed by the literature[31-33] and by a company-sought haematologist in Wales.

The model incorporates costs associated with: treatment acquisition and administration, disease management, adverse events, and end-of-life care. Idelalisib is associated with a Patient Access Scheme discount [commercial in confidence figure removed], which has been applied to the list price. The model further incorporates a relative dose intensity of 89.79%, as observed in study 101-09. No treatment costs are included in the model for best supportive care. However, treatment costs have been applied for chemotherapy-suitable patients. These are based on the different previous treatment strategies received by the 72 patients with follicular lymphoma in study 101-09. NHS reference costs have been used to cost chemotherapy administration[34]. Company estimates for disease management resource use have been guided by the ESMO 2014 Clinical Practice Guidelines[7] and verified by a clinical expert in Wales. Relapse-related management costs have been assumed and validated by one clinician consulted by the company. The cost estimates for palliative care are based on research from The King's Fund[35]. Likewise, adverse event costs have been informed by study 101-09[13]. NHS reference costs have mainly been applied to the resource use parameters[34].

In addition to those already mentioned, the economic analysis adopts several assumptions, including:

- Patient survival on best supportive care is assumed to be equal to post-progression survival in study 101-09.
- No progression-free survival for patients receiving best supportive care.
- Patients who die from all-cause mortality spend the last eight weeks of their life in the palliative care state.
- Adverse event rates for the cytotoxic comparators are assumed to be equivalent to those observed for idelalisib in study 101-09. The company considers this to be a conservative approach.

Univariate sensitivity and scenario analyses have been conducted to test the influence of uncertainty of individual parameters and structural assumptions on the robustness of the base case results. Sensitivity analyses explore the impact of changing each input to its upper and lower bound values. Scenario analyses additionally test the effect of: introducing utility decrements for pre- and post-progression to reflect that patients have follicular lymphoma that is double refractory and adjusting utility decrements for adverse events; altering TTP to reflect diminishing TTP with each additional line of chemotherapy; using the trial hazard ratio for pre-progression mortality; alternative discount rates; distributions and time horizon, among other factors.

4.1.2 Results

The results of the base-case analyses are detailed in Table 2. Idelalisib is reported to be more costly per patient than best supportive care and standard chemotherapy. However, idelalisib also generates greater quality-adjusted life year (QALY) gains.

The results of the univariate sensitivity analyses show that when idelalisib is compared with other cytotoxic treatments, the incremental cost-effectiveness ratio (ICER) is most sensitive to ToT for idelalisib and TTP. Table 3 details the scenario analyses that generated the most pronounced or noteworthy ICERs.

Table 2. Results of the base case analyses

	Idelalisib	Comparator treatment	Difference
Standard chemotherapy			
Total costs	¶¶	£36,447	¶¶
Total life-years	4.43	3.68	**0.75**
Total QALYs	3.00	2.37	**0.63**
ICER (£/QALY gained)	¶¶		
Best supportive care			
Total costs	¶¶	£28,306	¶¶
Total life-years	4.43	3.19	**1.24**
Total QALYs	3.00	1.97	**1.03**
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence figure removed
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year

Probabilistic sensitivity analyses show that at willingness-to-pay thresholds of £30,000, £40,000 and £50,000 per QALY gained, when compared with other chemotherapy regimens, idelalisib has a [commercial in confidence figures removed] chance, respectively, of being the most cost-effective treatment. When compared with best supportive care at these willingness-to-pay thresholds, idelalisib has a [commercial in confidence figures removed] chance, respectively, of being the most cost-effective treatment.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
Idelalisib versus standard chemotherapy		
Trial data hazard ratio applied to pre-progression mortality rate	¶¶	Given that this hazard ratio is based on a mere four observed events, this scenario is unlikely to offer a plausible alternative to the base case.
10% decrement of pre- and post-progression utility values	¶¶	As reported by the company, a clinical expert consulted by the company advised them that a 10% decrement is more realistic for patients whose disease is double refractory. As such, this scenario may be considered a plausible alternative to the base case.
Extreme value curve fit for post-progression survival	¶¶	A clinical expert who validated the model for the company suggested that this distribution may also reflect patient outcomes. Thus, this scenario may be also considered a plausible alternative to the base case.
Prior therapy split as informed by Welsh clinical expert	¶¶	This is a plausible alternative to the base case because it reflects company-sought clinical expert opinion in Wales.

Scenarios	ICER	Plausibility
Combination of prior therapy split as informed by Welsh clinical expert and 10% decrement of pre- and post-progression utility values	¶¶	AWTTC considers this to be a plausible alternative to the base case as it reflects company-sought clinical expert opinion in Wales. Probabilistic sensitivity analyses conducted by the company for this scenario reveal that at willingness-to-pay thresholds of £30,000, £40,000 and £50,000 per QALY gained, idelalisib has a [commercial in confidence figures removed] chance, respectively, of being the most cost-effective treatment.
Idelalisib versus best supportive care		
Trial data hazard ratio applied to pre-progression mortality rate	¶¶	Given that this hazard ratio is based on a mere four observed events, this scenario is unlikely to offer a plausible alternative to the base case.
10% decrement of pre- and post-progression utility values	¶¶	As reported by the company, a clinical expert advised them that a 10% decrement is more realistic for patients whose disease is double refractory. As such, this scenario may be considered a plausible alternative to the base case.
Extreme value curve fit for post-progression survival	¶¶	A clinical expert who validated the model for the company suggested that this distribution may also be reflective of patient outcomes. Thus, this scenario may be also considered a plausible alternative to the base case.
¶¶: commercial in confidence figure removed ICER: incremental cost-effectiveness ratio		

4.1.3 AWTTC critique

The base case ICER has been estimated at [commercial in confidence figure removed] per QALY gained versus other chemotherapy regimens, and [commercial in confidence figure removed] versus best supportive care. Collectively, it is uncertain that the company's base case analyses give robust ICER estimates. It is plausible that the ICER could exceed those reported in the base case comparisons. Analyses accounting for the joint uncertainty in parameter estimates show that the probability of the ICER estimates being below the threshold of £30,000 per QALY is [commercial in confidence figure removed] for the comparison with other chemotherapy regimens and [commercial in confidence figure removed] when compared with best supportive care. The model structure on which this estimate is based has the strength of being simple. However, there are several weaknesses and uncertainties in the economic analysis:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Justifications are provided for the assumptions applied in the model.
- A wide range of sensitivity and scenario analyses have been conducted.
- Efforts have been made to try to validate the model structure and extrapolations using clinical expert opinion.

Limitations:

- Study 101-09 lacked a comparator arm[13]. TTP data on previous treatment have therefore been used as a clinical outcome proxy for patients receiving comparator chemotherapy. However, these data are primarily based on clinician recall rather than formal assessment. This introduces the potential for significant uncertainty around effectiveness comparisons.
- The ICERs generated are highly sensitive to ToT and TTP. Since ToT and TTP probabilities used in the model are estimated via proxies, recall, assumptions,

and extrapolation, it is important to consider the related uncertainty and the impact this has on cost-effectiveness.

- The lack of mature data introduces considerable uncertainty surrounding longer term outcomes. Post-progression survival has been used instead of overall survival. Additionally, the predicted outcomes vary substantially depending on which parametric distribution is applied. Even though the company has sought to validate the choice of distribution, and has conducted a number of scenarios to address these issues, this does not remove the related uncertainties.
- A clinical expert approached by the company suggested that the distribution of patients across the different comparator chemotherapies in Wales is likely to be different to that seen in study 101-09[13]. While it was suggested that such differences would not impact on clinical outcomes, this nevertheless introduces uncertainty and the potential for bias, particularly regarding costs. The company has sought to explore this uncertainty via additional scenario analyses (see Table 3).
- The cost of idelalisib has been adjusted to incorporate the relative dose intensity observed in study 101-09[13]. This does not reflect prescribing practices, and consequently likely underestimates the costs associated with treatment acquisition. This approach has not been adopted for the chemotherapy comparators and introduces bias in the cost comparisons.
- The comparator drug acquisition costs did not include any subcutaneous rituximab; instead all rituximab has been costed as intravenous. AWTTC-sought clinical expert opinion suggested that subcutaneous rituximab is used in NHS Wales and that use was increasing. However, the proportion of subcutaneous to intravenous used in Welsh centres was not confirmed. The omission of subcutaneous rituximab has the potential to introduce cost bias, given that there is a cost difference and differences in how the medicine is administered. In addition, there is a patient access scheme in place in Wales for subcutaneous rituximab.
- The company acknowledges that the utility values used in the base case for pre- and post-progression are likely too high for this patient group, and have consequently conducted scenario analysis to test the impact of 10% utility decrements. The ICERs generated through these scenarios may arguably be considered more appropriate base cases.
- Using a general population mortality rate for pre-progression mortality is optimistic and adds further uncertainty to the model. While the company has explored the impact of this assumption via scenario analyses, there remains uncertainty about the full impact of this assumption, given the immaturity of the data used in the scenario analyses.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any cost-effectiveness studies focused on the treatment comparisons included in this submission for the population of interest.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that the prevalence and incidence of follicular lymphoma in Wales amount to ten and eight patients, respectively in year one. These figures have been calculated by applying follicular lymphoma or non-Hodgkin's lymphoma incidence proportions (n = 10.1%)[36] to reported non-Hodgkin's lymphoma prevalence rates[37] and Welsh population figures[38]. There is limited evidence to identify the proportion of these patients for whom chemotherapy is unsuitable. The company has therefore assumed that the proportion of patients receiving chemotherapy before entry into study 101-09

(n = 76%) acceptably represents the proportion for whom an additional line of chemotherapy is likely to be suitable[1]. Thus, 18 patients are considered to be eligible for active treatment for the indication under consideration in year one. In a world without idelalisib, approximately four of these patients would receive best supportive care and 14 would receive chemotherapy. The market share for idelalisib is projected to peak at [commercial in confidence figure removed] after two years, and then remain stable. The average duration of treatment with idelalisib is 6.9 months. A dose of two tablets of 150 mg per day is assumed. Patients are distributed over the other chemotherapies in keeping with the proportions in study 101-09[13]. The associated costs for these alterative chemotherapies are at their highest in weeks 1–4 (£523/week), and reduce over time, falling to £6 per week in weeks 25–32. After year 1 it is assumed that patients die at the same rate at which they reach eligibility. Given this, and the average duration of treatment, only 8 new patients are eligible for active treatment per year in years 2 to 5. The company also reports the costs of other resources, including: chemotherapy administration costs, adverse event management, pre-progression resource use, *Pneumocystis jirovecii* pneumonia prophylaxis, cytomegalovirus monitoring, and post-progression resource use[1]. Sensitivity analyses have been conducted to assess the impact of altering the assumptions made relating to the proportion of patients eligible for chemotherapy, and market uptake.

5.1.2 Results

The budget impact analyses are presented in Table 4. The introduction of idelalisib is reported to be associated with a positive budget impact ranging from [commercial in confidence figure removed] in 2017 to [commercial in confidence figure removed] in 2021. The introduction of idelalisib is also reported to impact on NHS resource use. This ranges from a resource saving of [commercial in confidence figure removed] in 2017, to a positive impact of [commercial in confidence figure removed] in 2021.

Table 4. Company-reported costs associated with use of idelalisib for the treatment of double-refractory follicular lymphoma

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible patients (as covered in this submission)	18	8	8	8	8
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treatment distribution in a market without idelalisib					
Number of patients treated with chemotherapy	13.7	6.1	6.1	6.1	6.1
Number of patients receiving BSC	4.3	1.9	1.9	1.9	1.9
Treatment distribution in a market with idelalisib					
Number of patients treated with idelalisib	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients treated with chemotherapy	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving BSC	¶¶	¶¶	¶¶	¶¶	¶¶
Costs					
Total medicine acquisition costs in market without idelalisib	£120,872	£53,721	£53,721	£53,721	£53,721
Total medicine acquisition costs in market with idelalisib	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition	¶¶	¶¶	¶¶	¶¶	¶¶

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
costs					
Supportive medicines costs	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net costs	¶¶	¶¶	¶¶	¶¶	¶¶
Cumulative net costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed BSC: best supportive care					

The sensitivity analyses showed that decreasing the proportion of patients eligible for chemotherapy to [commercial in confidence figure removed] increased the cumulative budget impact to [commercial in confidence figure removed] over five years (net resource costs for this period are estimated to be [commercial in confidence figure removed]. Assuming a [commercial in confidence figure removed] uptake in year 3 results in a cumulative budget impact of [commercial in confidence figure removed] over five years (net resource costs for this period are estimated at [commercial in confidence figure removed]). Finally, assuming a [commercial in confidence figure removed] peak uptake in year 5 results in a cumulative budget impact of [commercial in confidence figure removed] over five years (net resource savings for this period are estimated to be [commercial in confidence figure removed]).

5.1.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact.
- The estimates for uptake are based on company assumptions and are subject to uncertainty, as in all budget impact analyses.
- The company has assumed that patient mortality is equivalent to incident patients with no supporting evidence. This introduces uncertainty to the annual patient numbers included in the model.
- The medicines used to calculate the effects of market share displacement reflect those treatments received by patients in study 101-09. The resulting projections are therefore subject to a degree of uncertainty, particularly given that company-sought clinical expert opinion identified a different mix of treatments in this patient group.
- Costs are derived from the economic model, therefore the limitations of the economic model apply to the budget impact estimates.
- The budget impact relies heavily on a number of assumptions, thus collectively creating uncertainty for the overall budget impact predictions.

5.2 Comparative unit costs

Table 5 provides examples of medicines that could potentially be used in people with double-refractory follicular lymphoma.

Table 5. Examples of medicine acquisition costs

Regimens	Example doses per cycle or 28 days*	Costs per patient per cycle
Idelalisib	150 mg orally twice daily for 28 days*	£2,907
Rituximab monotherapy[39]	375 mg/m^2 IV once weekly for 4 weeks	£5,003
R-CHOP[40]	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,486

Regimens	Example doses per cycle or 28 days*	Costs per patient per cycle
RB[41]	Rituximab 375 mg/m^2 IV on day 1, bendamustine 90mg/m^2 IV on days 1 and 2 of a 4-week cycle	£1,346
R-CVP[42]	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 100 mg on days 1–5, every 21 days	£1,309
CHOP[40]	Cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 40 mg/m^2 on days 1–5, every 21 days	£234
RP[40]	Rituximab 375 mg/m^2 IV, on day 1; oral prednisolone 40 mg/m^2 on days 1–5, every 21 days	£1,256
RCHO[40]	Rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1, every 21 days	£1,481
CVP[42]	Cyclophosphamide 750 mg/m^2 IV, vincristine 1.4 mg/m^2 (max dose 2 mg) IV all on day 1; oral prednisolone 40 mg/m^2 on days 1–5, every 21 days	£58
F-RC[43]	Rituximab 375 mg/m^2 IV on day 1, cyclophosphamide 120 mg/m^2 orally on days 1–4, fludarabine 25 mg/m^2 orally on days 1–4	£1,661
CHPE[44]	Cyclophosphamide 600 mg/m^2 IV on day 1, doxorubicin 25 mg/m^2 IV on day 1, etoposide 100 mg/m^2 IV on day 1, and prednisolone 40 mg/m^2 orally on days 1–5	£135
R-Ch[45]	Rituximab 375 mg/m^2 IV on day 1, chlorambucil 10 mg/day orally for 10 days, for a 28-day cycle	£1,337
CHOEP[46]	CHOP with etoposide 100 mg/m^2 on days 1–3 of 21-day cycle	£301
CHEPi[47]	CHPE with interferon alpha 5 million IU three times weekly in a 21-day cycle	£384
ChP[48]	Chlorambucil 10 mg orally once daily on days 1–14, prednisolone 40 mg orally once daily on days 1–14, cycle length 4–8 weeks.	£125
FMD[49]	Fludarabine 40 mg/m^2 orally on days 1–3, mitoxantrone 10 mg/m^2 IV on day 1 and dexamethasone 20 mg orally on days 1–5 of a 28-day cycle	£630

*costs are given per cycle for all regimens except idelalisib; for idelalisib cost given is for 28 days of treatment.
IV: intravenous
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details.
Costs are based on Monthly Index of Medical Specialities (MIMS) and British National Formulary list prices as of November 2016, assuming vial sharing and zero wastage.
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, idelalisib (Zydelig®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months. Real world data are expected to be published in early 2017 from an early access programme involving 73 patients in the UK[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 31 October 2016 and 1 November 2016.
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

The applicant company has indicated that idelalisib may be considered under the AWMSG policy for appraising life-extending, end-of-life medicines[50]. The AWMSG criteria for appraising life-extending, end-of-life medicines, and a discussion of the extent to which idelalisib may meet these criteria, are provided in Table 6.

Table 6. End-of-life considerations for New Medicines Group (NMG)/AWMSG

AWMSG criteria for application of the End-of-life policy (all must apply)[34]	Idelalisib considerations
The most plausible ICER estimate exceeds £30,000 per QALY gained	The base case ICER presented by the company versus standard chemotherapy is [commercial in confidence figure removed] per QALY gained. Probabilistic sensitivity analysis estimates that the likelihood of idelalisib being cost-effective at a £30,000 WTP threshold when compared with other cytotoxic therapy is 25%. When a utility decrement is applied to best supportive care, this also increases the ICER above £30,000 per QALY gained. AWTTC therefore estimates that the most plausible ICERs are likely to meet this criterion.
The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).	The pivotal trial is a phase II open-label single-arm study therefore there are no data available to determine median survival in a control group. The company claims that the general consensus in the clinical community is that median overall survival does not typically exceed two years in patients with double-refractory follicular lymphoma. However, data to support this are limited and no further evidence has been submitted by the company. AWTTC-sought clinical expert opinion suggests that prognosis for patients with double-refractory follicular lymphoma is poor. Overall life expectancy for this group of patients depends on a number of factors and therefore there is some uncertainty as to whether this criterion is met.
There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression-free survival or overall survival.	Median overall survival in the pivotal study (101-09) of double-refractory indolent non-Hodgkin's lymphoma patients (which included 72 of 125 patients (58%) with follicular lymphoma) was 30.8 months[13]. The median overall survival in the subgroup of patients with follicular lymphoma was not reached. In the company's model extrapolation of the study data was used to determine an incremental difference in projected life years gained versus standard therapy of 0.75 years or 9 months.
ICER: incremental cost-effectiveness ratio (incremental cost per QALY gained); QALY: quality-adjusted life years; WTP: willingness to pay	

If NMG and AWMSG conclude that idelalisib should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines, NMG and AWMSG will need to consider:

- The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age. Using the company's base case versus standard chemotherapy analysis (0.75 life years saved), together with age-standardised utility based on

the median age of patients in the pivotal study (0.78)[51] leads to a weight of [commercial in confidence figure removed] using a threshold of £30,000/QALY gained.

- The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the medicine to fall within the current threshold range. Using the company's base case ICER versus standard therapy [commercial in confidence figure removed] and the threshold of £30,000/QALY leads to a weight of [commercial in confidence figure removed].

In addition, NMG and AWMSG will need to be satisfied that:

- the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review); and
- the assumptions used in the economic modelling are plausible, objective and robust.

6.6 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The company claims that the medicine meets the criteria for an ultra-orphan medicine. Idelalisib does not have EMA-designated orphan status, but AWTTC considers that idelalisib is eligible to be considered as a medicine developed specifically for rare diseases, i.e. the full population of the licensed indication is likely to be below the 5 in 10,000 persons (or 1,500 patients in Wales) threshold[52]. For medicines developed specifically to treat a rare disease, NMG and AWMSG may consider additional criteria for appraising these medicines (see Table 7), if the cost per QALY is above the normal thresholds applied.

Idelalisib is currently licensed for the treatment of double refractory follicular lymphoma and for chronic lymphocytic leukaemia. The company estimates a total eligible population of 18 people with double-refractory follicular lymphoma per year in Wales (see section 5.1.1). Idelalisib is also indicated for some people with chronic lymphocytic leukaemia first-line in those with a 17p deletion or a TP53 mutation in people who are not eligible for any other therapies and for people with relapsed disease who have received at least one previous therapy. The company reports that in 2013, there were 229 people with chronic lymphocytic leukaemia eligible for treatment in Wales[53] and 154 of these (67%) would be expected to need treatment[54]. The company estimates that 7.5% of this population will have a 17p deletion or TP53 mutation, giving 12 people eligible for treatment. Company market research suggests that 19% of 154 people relapse after first-line treatment, giving a further 29 people. Thus, 41 people with chronic lymphocytic leukaemia are eligible for idelalisib. Therefore, the company estimates that the total population eligible for idelalisib would be 18 people with follicular lymphoma plus 41 people with chronic lymphocytic leukaemia, giving a total of 59 people who would be eligible.

Table 7. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	The applicant company highlights that follicular lymphoma is a chronic, incurable disease characterised by a recurring and remitting course over several years. Each relapse becomes more difficult to treat and each remission becomes shorter than the previous one. As the disease progresses treatments become less effective and survival rates decrease. Most patients eventually die of this disease[27]. A 1995 study reported that overall survival in patients who received third-line treatment was less than two years (although this was before the introduction of rituximab)[55] Follicular lymphoma is associated with physical and psychological symptoms that affect people's quality of life including fatigue, weight loss, fever and night sweats[27]. Enlarged lymph nodes can lead to restricted movement, disfigurement and pain[27]. Chemotherapy treatment can additionally reduce quality of life which may be worse than the disease itself[27], resulting in activity impairment, anxiety and depression and loss of productivity.
Whether medicine addresses an unmet need (e.g. no other licensed medicines)	The company advises that there is no clearly defined therapeutic approach for standard of care in patients with double refractory follicular lymphoma. A trial and error approach with repeated cycles of chemotherapy, upon which the patient's disease has already relapsed or become refractory to, is the only alternative to best supportive care. For people who cannot tolerate chemotherapy and for those who are not fit for stem cell transplant, idelalisib gives an alternative option to best supportive care.
Whether the medicine can reverse or cure, rather than stabilise the condition.	The company states that idelalisib does not reverse or cure follicular lymphoma.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development.	There is currently no curative pharmacological therapy in development. However, the company report that some clinicians have suggested idelalisib may have the potential to act as a bridge to stem cell therapy in a small population of fitter people with follicular lymphoma. However, no specific evidence has been provided and this use is outside the current license.
The innovative nature of the medicine.	Idelalisib has an innovative mode of action, is an oral medicine and is not chemotherapeutic.
Added value to the patient which may not be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	The company suggests that idelalisib may allow some people to return to normal living. The treatment may result in fewer people receiving intravenous chemotherapies which are burdensome in terms of time and resource for patients, carers and the NHS.
Added value to the patient's family (e.g. impact on a carer or family life).	Follicular lymphoma places a substantial burden on carers; a study in Canada in people with follicular lymphoma or indolent non-Hodgkin's lymphoma showed that unpaid carers provided a mean of 9.8 days of care in a 30-day period[56], however specific UK or Wales data have not been provided.
QALY: quality-adjusted life year	

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