**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia**

**Response to consultee and commentator comments on the draft remit and draft scope**

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

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Wording | AbbVie | Yes | Comment noted. No change to the scope required. |
| Leukaemia Care | It is hard to answer this at this stage as the EMA UK marketing authorisation decision has not yet been issued and therapeutic indication defined. | Comment noted. No change to the scope required. |
| Chronic Lymphocytic Leukaemia Support Association (CLLSA) | Yes | Comment noted. No change to the scope required. |
| UK CLL FORUM, BSH, RCPath | Yes | Comment noted. No change to the scope required. |
| Timing Issues | AbbVie | The NHS would benefit from early appraisal of this technology as there are limited treatment options in untreated CLL | Comment noted. This appraisal has been scheduled into the technology appraisal work programme. |
| Leukaemia Care | Patients who are unsuitable for 1st line therapies, such as FCR or bendamustine, urgently require access to treatments, preferably of a limited duration and those that are able to offer a deep and durable response and good quality of life. | Comment noted. This appraisal has been scheduled into the technology appraisal work programme. |
| CLLSA | Some urgency for this appraisal | Comment noted. This appraisal has been scheduled into the technology appraisal work programme. |
| UK CLL FORUM, BSH, RCPath | This is an important innovation in front line treatment for CLL, this treatment would fill the gap for the patients not suitable for chemoimmunotherapy. | Comments on innovation noted. The committee will consider the innovative nature of the technology during the course of the appraisal. |

Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Background information | AbbVie | Currently the draft scope describes the disease but does not reference the unmet clinical need in untreated CLL. For completeness, the unmet clinical need should be included in the scope.  Currently, the draft scope does not include a brief description on the prognostic significance of del/(17p) or TP53 mutation and the higher risk associated with this sub-population. | Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and treatments currently used in the NHS. The scope has been updated to briefly describe the del(17p) and TP53 mutations. |
| CLLSA | Many patients will never need treatment and the number of patients likely to need and benefit from this treatment are significantly less than the number of cases each year. | Comment noted. The background section has been updated. |
| UK CLL FORUM, BSH, RCPath | The recommended standard of care for untreated CLL as outlined in the 2018 BSH guideline (British Journal of Haematology, 2018, 182, 344-359) is as follows: fludarabine cyclophosphamide rituximab (FCR) is recommended as initial therapy for fit patients and bendamustine+ rituximab is an acceptable alternative for fit patient for whom FCR is contraindicated due to comorbid conditions. Front-line treatment for less fit patients currently is chlorambucil + obinutuzumab (ofatumumab option has been withdrawn from non-US market in January 2018). Chlorambucil + rituximab is not routinely recommended; bendamustine+ rituximab might be considered as an alternative  Venetoclax Obinutuzumab would fit as an option for frontline treatment alongside FCR, BR and Chlorambucil+ Obinutuzumab  We anticipate that venetoclax+ obinutuzumab in front line is likely to be superior to current standard of care | Comments noted. The treatment options are already included in table 1 of the background section. No change to the scope required. |
| The technology/ intervention | AbbVie | The description of the pivotal phase 3 trial that is being used to support the marketing authorisation application for venetoclax with obinutuzumab is incorrect. Please change to “*It is being studied in clinical trials in comparison with ~~standard chemo-immunotherapy (FCR and BR) and~~ obinutuzumab with chlorambucil, in adults with untreated CLL*”  The CLL14 trial <https://www.nejm.org/doi/full/10.1056/NEJMoa1815281> compared venetoclax plus obinutuzumab treatment with chlorambucil plus obinutuzumab in previously untreated patients with CLL and comorbidities | Thank you for your comment. The technology section has been updated. |
| CLLSA | Yes | Comment noted. No change to the scope required. |
| UK CLL FORUM, BSH, RCPath | Yes | Comment noted. No change to the scope required. |
| Population | AbbVie | The population is defined appropriately | Comment noted. No change to the scope required. |
| Leukaemia Care | The CLL 14 trial data investigated the treatment of venetoclax and obinutuzumab in 1st line patients with previously untreated CLL and coexisting conditions; therefore, we anticipate that the population will be redefined to cover just these patients. The rest of the comments in this document are based on this assumption.  This included a significant population of patients with a TP53 deletion or mutations. This population is automatically ineligible for the chemotherapeutic options and so are in need of new options. | The population has been kept broad to ensure that it captures the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. |
| CLLSA | Yes | Comment noted. No change to the scope required. |
| UK CLL FORUM, BSH, RCPath | We do support a broad approval for Venetoclax with Obinutuzumab in the untreated population.The CLL14 trial looked at all patients in the untreated population who have a CIRS score ≥6 as this was appropriate for the comparator but we favour a broad appraisal of the entire cohort. Subsequent subgroup analyses have indicated particular benefit for those patients who have an unmutated IGHV, for whom chemo-immunotherapy (FCR, BR or Chlorambucil based) fails to induce lasting remissions and this subgroup would likely particularly benefit from this regimen.  FCR is effective in the IGHV mutated group of CLL patients, but is unsuitable for those with reduced marrow reserve, reduced renal function or other comorbidities – patients do significantly worse with a fludarabine based regimen if they have 2 or more co-morbidities (Goede V et al. Haematologica 2014;99:1095-1100). The average CLL patient aged between 55 and 64 has 2.9 co-morbidities (Yancik R. Cancer 1997; 80: 1273—1283) rising to 4.2 for those over 75. There is also need to improve on FCR in frontline treatment of IGH unmutated CLL  Therefore clinicians should have flexibility where possible when choosing the “best” tailored therapy for an individual patient and be able to discuss options with patients and involve them in the decision making process. | Comment noted. The population has been kept broad to ensure that it captures the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. |
| Comparators | AbbVie | Without a del(17p) or TP53 mutation:  AbbVie agree that **obinutuzumab with chlorambucil** can be considered a comparator to venetoclax with obinutuzumab. However, the following combinations are not comparators:   * **FCR**: The CLL14 trial population <https://www.nejm.org/doi/full/10.1056/NEJMoa1815281> excludes patients who would normally be eligible for FCR and therefore the evidence submission to NICE would be for FCR ineligible patients. * **BR**: According to the BSH guidelines on CLL (2018) <https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15460> BR is recommended as an alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions. BR is not a comparator as the evidence submission is for unfit patients only. * **Chlorambucil with rituximab**: According to the BSH guidelines on CLL (2018) “*Chlorambucil in combination with rituximab is not routinely recommended (GRADE IB)*” and can therefore not be considered a comparator * **Ofatumumab with chlorambucil**: According to NICE, <https://www.nice.org.uk/guidance/ta344> the guidance for TA344 has been withdrawn because Novartis has discontinued ofatumumab. Therefore, ofatumumab with chlorambucil is not a comparator for this appraisal.   With a del(17p) or TP53 mutation:  AbbVie agree that **ibrutinib** can be considered a comparator to venetoclax with obinutuzumab. However, the following combination is not a comparator:   * **Idelalisib with rituximab**: The clinical consensus is that ibrutinib has superseded idelalisib with rituximab as the BCRI of choice. Page 6, section 3.2 of TA561<https://www.nice.org.uk/guidance/ta561> [Feb 2019] states that *“…most people have ibrutinib rather than idelalisib plus rituximab, because idelalisib plus rituximab has an intensive dosing regimen and is associated with increased risk of infection*” Furthermore the BSH guidelines on CLL (2018) states that “…*ongoing pharmacovigilance revealed a higher risk of infection and death with idelalisib therapy than previously noted (Lampson et al, 2016), leading the European Medicine Agency (EMA) to review its license for idelalisib, and to recommend idelalisib for “first-line treatment of CLL in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies*” Therefore idelalisib with rituximab is not a comparator for this appraisal. | Comment noted. The remit and therefore the comparators in the scope have been kept broad to ensure they capture the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. The company can outline how it intends to approach the decision problem when invited to prepare the STA evidence submission. See section 3.2.2 of NICE’s ‘Guide to the processes of technology appraisal’ available at <https://www.nice.org.uk/process/pmg19/chapter/the-appraisal-process>  The comparators section has been updated to reflect that ofatumumab has been discontinued in the UK. |
| Janssen-Cilag | The comparators listed in the draft scope accurately reflect the standard treatments currently used in the NHS for the untreated chronic lymphocytic leukaemia (CLL) population with the exception of the combination of chlorambucil with ofatumumab, as ofatumumab no longer holds a market authorisation in the European Union.[[1]](#footnote-1)  https://www.ema.europa.eu/en/medicines/human/EPAR/arzerra | Thank you for your comment. The comparators section has been updated to reflect that ofatumumab has been discontinued in the UK. |
| Leukaemia Care | Fludarabine, cyclophosphamide and rituximab (FCR), and bendamustine with or without rituximab (BR) are not suitable comparators as these are treatments unsuitable for unfit patient, such as those with comorbidities.  Ofatumumab with rituximab is not a suitable comparator as is no longer in clinical use in UK. Novartis withdrew ofatumumab for CLL from markets outside the US due to low numbers of patients using the treatment. (Ref: https://www.sps.nhs.uk/medicines/ofatumumab)  As a significant number of CLL14 trial patients were TP53 mutated or deleted, ibrutinib should be considered a comparator as this is the treatment in routine use for this subgroup. However, idelalisib plus rituximab is not often used in UK practice currently due to immune related challenges. | Comment noted. The remit and therefore the comparators in the scope have been kept broad to ensure they capture the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. The comparators section has been updated to reflect that ofatumumab has been discontinued in the UK. |
| CLLSA | If all untreated patients are to be considered then the comparators are correct. It should be noted that Chlorambucil with or without Rituximab is not generally used.  Bendamustine is being less frequently used. | Comment noted. The remit and therefore the comparators in the scope have been kept broad to ensure they capture the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. |
| UK CLL FORUM, BSH, RCPath | The comparators listed in the draft scope for patients without a 17p deletion or TP53 mutation are fludarabine+ cyclophosphamide+ rituximab (FCR), bendamustine+ rituximab (BR), chlorambucil+ rituximab, obinutuzumab + chlorambucil and ofatumumab + chlorambucil.  This is comprehensive list of treatment options with the exception of the ofatumumab + chlorambucil combination; ofatumumab has been withdrawn from the market by Novartis in January 2018 <https://www.sps.nhs.uk/medicines/ofatumumab/>.  Obinutuzumab in combination with chlorambucil has been appraised by NICE TA343 and published on 2nd June 2015; the decision was reviewed in September 2018. The overall survival data of the German CLL11 trial has been updated at the European haematology Association 2018 Congress, OS was also improved with obinutuzumab/chlorambucil. OS was not reached with obinutuzumab+chlorambucil; it was 73.1 months with rituximab+chlorambucil (HR, 0.76; 95% CI, 0.60 - 0.97; P = .0245).  Survival rates in the obinutuzumab+chlorambucil and rituximab+chlorambucil arms were 91% vs 84% *at 2 years and 66% vs 57% at 5 years. There were significantly fewer deaths overall in the obinutuzumab/chlorambucil group (37% vs 45%)* | Comment noted. The remit and therefore the comparators in the scope have been kept broad to ensure they capture the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. The comparators section has been updated to reflect that ofatumumab has been discontinued in the UK. |
| Outcomes | Leukaemia Care | MRD status should be considered as an outcome. Having undetectable MRD in the blood or bone marrow is an important treatment objective in patients with CLL and is associated with prolonged PFS and overall survival. | Comment noted. Other clinically relevant outcomes may be included in the company’s submission provided sufficient rationale is given to support direct health effects for patients. No changes to the scope required. |
| CLLSA | Consider assessment of minimal residual disease as a surrogate marker for effectiveness. | Comment noted. Other clinically relevant outcomes may be included in the company’s submission provided sufficient rationale is given to support direct health effects for patients. No changes to the scope required. |
| UK CLL FORUM, BSH, RCPath | In addition to listed outcome measures we would also recommend adding “health care utilisation“, although not routinely collected as part of clinical trials, it is important to look as part of overall cost considerations in looking at comparators.  MRD status could be considered to be an appropriate outcome measure. | Comment noted. Other clinically relevant outcomes may be included in the company’s submission provided sufficient rationale is given to support direct health effects for patients. No changes to the scope required. |
| Economic analysis | CLLSA | Yes | Comment noted. No change to the scope required. |
| Equality and Diversity | CLLSA | No issues identified at this stage | Comment noted. No change to the scope required. |
| UK CLL FORUM, BSH, RCPath | No issues | Comment noted. No change to the scope required. |
| Other considerations | AbbVie | This should be amended to: “*If the evidence allows the following subgroups will be considered:*   * *people with untreated CLL with****~~out~~*** *del(17p) or TP53 mutation”*   People with del/(17p) or TP53 mutation are the sub-population of interest due to the higher risk profile. | Comment noted. The scope has been updated. |
| Janssen-Cilag | In addition to the two subgroups listed in the draft scope (“people with untreated CLL without del(17p) or TP53 mutation”; “people with untreated CLL for whom fludarabine-based therapy is unsuitable)”, the following subgroup should be considered: “people with untreated CLL for whom bendamustine-based therapy is unsuitable”.  There are two reasons for this:   1. to accurately reflect the full list of comparators in the draft scope and more specifically chlorambucil with or without rituximab/obinutuzumab;   to be aligned with NICE TA343 that states that chlorambucil with obinutuzumab is recommended for untreated CLL patients if “bendamustine-based therapy is not suitable”. | Comment noted. The scope has been updated. |
| Innovation | AbbVie | There are limited options for untreated CLL.  Chlorambucil based chemo-immunotherapy has been the back bone of untreated CLL without a del(17p) or TP53 mutation in patients who are unfit for FCR. However, there is an unmet need for a broader range of therapeutic options with a different mechanism of action that are effective and can provide deep responses.  The advent of B Cell receptor inhibitors (BCRi) such as ibrutinib has reduced the reliance on toxic chemo- based regimens in untreated CLL with a del(17p) or TP53 mutation. However, there is a high unmet need in patients with cardiac risk factors who cannot tolerate ibrutinib. Furthermore, there is a high unmet need for treatments with alternative mechanisms of action  Venetoclax is a first-in-class, oral, selective inhibitor of BCL-2, with a unique targeted mechanism of action that distinguishes it from other available therapies.  As demonstrated in the CLL14 trial, venetoclax in combination with obinutuzumab has the potential to further improve the range of treatment options and provides substantial health-related benefits in the form of:   * **Fixed treatment duration chemo-free therapy**, enabling significant proportions of patients prolonged time without therapy, reducing the overall significant cost burden of therapy, especially when contrasted to daily, treatment-to-progression alternative therapies such as BCRIs * **Avoids the need for chemo-immunotherapy,** which creates mutations/clonal evolution * **Manageable side effect profile** * **Significant rates of undetectable Minimal Residual Disease (MRD)** being achieved from a targeted, chemo-free therapy combination, indicating deep responses to treatment | Comments on innovation noted. The committee will consider the innovative nature of the technology during the course of the appraisal. |
| Leukaemia Care | Yes, this is a first or a step change for CLL treatment front-line for patients who are ineligible for chemotherapy. The unique aspects of this treatment is that it is a targeted, non-chemotherapy, combination treatment of a fixed duration, achieving high levels of MRD negativity/undetectable in a population which historically have been hard to treat.  It also offers an alternative to a continuous therapy for those with a TP53 deletion or mutation, and therefore potentially a break from treatment side effects, which patients see as particularly important in terms of quality of life. | Comments on innovation noted. The committee will consider the innovative nature of the technology during the course of the appraisal. |
| CLLSA | Yes.  This is a uniquely novel treatment which provides unmatched, very deep response rates with a fixed duration of treatment. | Comments on innovation noted. The committee will consider the innovative nature of the technology during the course of the appraisal. |
| UK CLL FORUM, BSH, RCPath | Yes, Venetoclax is easy to administer (after the escalation phase) has a good side effect profile: has not been associated with increased infection rates and prophylactic antibiotic treatment is not considered necessary.  Venetoclax and venetoclax combination therapy are able to induce MRD (Minimal Residual Disease) negative responses. In the context of patients receiving chemoimmunotherapy, it is now clear that MRD-negativity is a predictor of both PFS and OS in both frontline and relapsed refractory settings (Kwok M et al. Blood 2016; 128: 2770–2773 and Dimier et al Blood. 2018 Mar 1;131(9):955-962), it is expected that non-chemoimmunotherapy treatment inducing MRD negativity will have the same effect on overall survival.  Venetoclax combination therapy is a very well tolerated treatment, patients enjoy good quality of life.  During QALY calculation the serious side effects of immunosuppression and myelotoxicity of FCR and BR should be considered | Comments on innovation noted. The committee will consider the innovative nature of the technology during the course of the appraisal. |
| Questions for consultation | AbbVie | The anticipated position of venetoclax with obinutuzumab is frontline for untreated CLL in patients:   * Without a del(17p) or TP53 mutation and who are unfit for FCR * With a del(17p) or TP53 mutation | Comment noted. No change to the scope required. |
| Janssen-Cilag | Q: Which treatments are considered to be established clinical practice in the NHS for untreated chronic lymphocytic leukaemia?  Comment: As per comment above, all treatments listed in the draft scope “comparator” section are relevant with the exception of chlorambucil with ofatumumab.  Given that treatment algorithms from recently published national and European/international guidelines2,3,4 take into account patients’ fitness level to define treatment options in the untreated CLL population, stratification of the draft scope treatment options based on this criteria would clarify the range of comparators for each potential subgroup of the population with no del17p/TP53 mutation:   * Fit = rituximab with fludarabine and cyclophosphamide (FCR) * Fit with comorbidities [patients ineligible for FCR] = bendamustine with or without rituximab (BR)   Unfit with comorbidities [patients ineligible for BR] = chlorambucil with or without rituximab/obinutuzumab 2 https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.154603 https://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations4 NCCN Guidelines – CLL/SLL - V5.2019 (May 23, 2019) | Comments noted. The remit and therefore the comparators in the scope have been kept broad to ensure they capture the whole possible population that may be included in the wording of the marketing authorisation from the European Medicines Agency. No change to the scope required. |
| UK CLL FORUM, BSH, RCPath | It will be important to obtain updated results of MRD negativity and overall survival data on CLL14 as they mature.  Another much anticipated study which is expected to be completed in February 2021 is the Janssen - sponsored GLOW study, an open-label, phase 3 study of the combination of ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab for the first-line treatment of subjects with CLL/SLL https://clinicaltrials.gov/ct2/show/NCT03462719. Ibrutinib Venetoclax combination in GLOW is given for 15 months. | Comment noted. During the development of the appraisal, the company will provide data as part of its submission and this will be considered at the appraisal committee meeting. |

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

# Lymphoma Action

Sanofi

Roche

1. https://www.ema.europa.eu/en/medicines/human/EPAR/arzerra [↑](#footnote-ref-1)