National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Duvelisib for treating relapsed or refractory chronic lymphocytic leukaemia after at least 2 prior treatments

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

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	CLL Support and Lymphoma Action	Yes	Comment noted. No action needed.
	UK CLL Forum	Yes. See section on “Background”	Comment noted. No action needed.
	Secura Bio Limited	The remit should reflect the detail of the approved indication which specifies that duvelisib is authorised for use “after at least two prior therapies”. Suggest amending the remit to “To appraise the clinical and cost effectiveness of duvelisib within its marketing authorisation for treating relapsed or refractory chronic lymphocytic leukaemia after at least two prior therapies.”	Thank you for your comments. The remit and title have been amended.

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Timing Issues	CLL Support and Lymphoma Action	There is an urgent need for new treatments for CLL because it is a heterogeneous disease affecting older people with a variety of pre existing co-morbidities.	Comment noted. No action needed.
	Leukaemia Care	For patients that have failed and are resistant to other targeted therapies, duvelisib may be considered as a last resort treatment. Although, it is important to note there is already a PI3K kinase inhibitor (idelalisib) available if a clinician feels this is the best option.	Comment noted. No action needed.
	UK CLL Forum	Patients with CLL are now (2020) relapsing having received Ibrutinib and/or venetoclax without any treatment option. This means that finding a viable 3rd line agent in CLL is urgent and pressing in the NHS.	Comment noted. No action needed.
	Secura Bio Limited	As patients relapse or become refractory to treatment, outcomes worsen and costs increase. Adopting duvelisib within the NHS will ameliorate this economic and patient burden.	Comment noted. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	CLL Support and Lymphoma Action	High risk CLL also includes patients who do not have TP53 mutations or 17p deletion but are high risk because of complex karyotype and/or unmutated IgHV status.	Comment noted. No action needed.
	UK CLL Forum	The background information is over simplified and only partially correct. Clarify that the “white blood cells” are Lymphocytes. The bone marrow appearance is typically characterised by heavy infiltration by mature but malignant lymphocytes which can cause bone marrow failure. This	Comment noted. The background section of the scope is intended to provide a brief summary of the

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		means that production of normal constituents of the blood is reduced leading to anaemia and low platelets. The background indicates swollen glands in neck, armpit or groin. The disease may not be limited to these sites. All lymph node areas can be affected including intrathoracic or intraabdominal nodes. Extralymphatic infiltration eg skin or ocular may occur. In addition to the symptoms already listed, patients may also experience fevers, sweats and weight loss. We would recommend that reference is made to the standard criteria for indication to treat CLL (IWCLL Criteria, Hallek et al Blood 2018) which are used both in the front line and relapse setting. The background is right to highlight the significance of TP53 alteration. It would be appropriate to state specifically that patients with a TP53 alteration are resistant to chemoimmunotherapy (see also 'Population' section below). The risk of high grade (Richter's) transformation is not mentioned which may be increased in CLL with TP53 alteration. The statement that "The presence of an immunoglobulin heavy chain gene (IGHV) mutation may also affect clinical outcomes" could better read "Unmutated IGHV genes are associated with shorter time to first treatment and may affect duration of response, especially in patients treated with chemo-immunotherapy." The factors affecting treatment in the background importantly omit TP53 status. This is the single most significant predictor of response to therapy and a crucial factor in determining therapeutic choices. The list of current treatment options for treated CLL in Table 1 does not include TA 487, venetoclax monotherapy.	condition. The draft scope has now been updated to reflect that: • The white blood cells affected are lymphocytes. • All lymph node areas can be affected. Venetoclax monotherapy (TA487) was recommend as a treatment option in the Cancer Drugs Fund (CDF) and therefore not considered appropriate as a comparator in this appraisal. Please see the NICE position statement on CDF treatments as comparators
	Secura Bio	The background section rightly emphasises the complexity of treating relapsed or refractory CLL, with previous treatments cited as a factor. It is worth noting in this context that 4 out of 5 treatment options listed	Thank you for your comment. The committee will only be able to make

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		include rituximab and therefore options for patients who have failed on rituximab-containing regimens in later line CLL are extremely limited.
		Based on its approved indication and on clinical expert opinion[1], the anticipated position in the CLL treatment pathway for duvelisib is:
		• After two prior therapies:
		  ○ as an alternative mechanism of action after a BTKi and a BCL-2i (separately or in combination); or
		  ○ after at least one rituximab-containing regimen; or
		  ○ where one of the above has failed and the others are contra-indicated (e.g. because of cardiac risk);
		• As an oral monotherapy, in preference to idelalisib + rituximab, saving the NHS costs and the patient potential treatment delay arising from challenges in scheduling IV infusion, or where the patient is elderly or otherwise less mobile and the need for hospital or physician office visits ought to be minimised;
		• As an option for bridging therapy between front line treatment and allogeneic stem cell transplant, in transplant-suitable patients.
			recommendations in line with the marketing authorisation. The company's rationale for a specific position for duvelisib should be made clear in its submission. No action needed.

The technology/ intervention	CLL Support and Lymphoma Action	Yes	Comment noted. No action needed.
	UK CLL Forum	The description of the technology is minimal and should specifically include that the PI3Kinase pathway is downstream of the B cell receptor, which is fundamental in the pathogenesis of CLL. PI3K inhibitors have been shown block cell growth and induce cell death in vitro.	Comment noted the technology description section is intended to provide a brief summary of the

[1] England & Wales CLL HCP Advisory Board, held on 17th June 2021

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			technology. No change required.
	Secura Bio Limited	One correction: as of 26th May 2021, duvelisib has an MHRA marketing authorisation for chronic lymphocytic leukaemia	Comment noted. The technology section has been amended.
Population	CLL Support and Lymphoma Action	Yes	Comment noted. No action needed.
	Leukaemia Care	This could be an option for those in whom other new agents (BTK inhibitors, venetoclax etc.) are unsuitable, or in those who are unable to have first line treatment and so have fewer options over the course of their disease, although, as previously mentioned, idelalisib is available in that population already.	Comment noted. The appraisal committee are only able to make recommendations for populations included in the marketing authorisation. No action needed.
	UK CLL Forum	It is possible that there may be patient groups who would be inappropriately excluded from the population as it is currently defined. Patients with and without TP53 alteration should be treated as different populations, allowing for the reduced number of treatment lines available to patients with TP53 alteration. Specifically, the presence of TP53 alteration precludes the use of ChemoImmunotherapy and therefore reduces by at least one, the number of lines of prior therapy before duvelisib treatment could be appropriate. A patient with TP53 alteration with a contra-indication to BTK inhibitor may only have received single agent venetoclax as first	Comment noted. The scope has been updated to include people with or without TP53 alteration as subgroups that will be considered if the evidence allows. NICE are only able to make recommendations for populations included in the marketing authorisation as such any potential NICE guidance would not

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		line treatment, butwould be precluded from Duvelisib as second line therapy, according to this draft scope. Even in the absence of a TP53 alteration, it is important to appreciate that many patients in the UK will have received treatment on the FLAIR frontline clinical study. >50% of patients on this study will not have received any form of chemo-immunotherapy at relapse, and at present, in the NHS these patients are eligible to receive Venetoclax Rituximab at first relapse. Such patients may therefore have received two or more lines of therapy which will not include chemo-immunotherapy and we would not wish to see such patients excluded from being considered.	necessarily preclude people who have not received chemo-immunotherapy as long as they had received at least two prior therapies. No action needed.
	Secura Bio Limited	The population is appropriately defined.	Comment noted. No action needed.
Comparators	CLL Support and Lymphoma Action	We consider bendamistine with or without rituximab or Rituximab with fludarabine and cyclophosphamide are NOT suitable comparators as it is unlikely that they would be used in this setting of two prior treatments. Venetoclax with rituximab could be described as ‘best alternative care’	Thank you for your comment. The list of comparators has been amended, rituximab with fludarabine and cyclophosphamide has been replaced with a broader chemoimmunotherapy option. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness

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			evidence and current clinical practice.
	Leukaemia Care	FCR is not a good comparator, unlikely to be considered after two prior therapies.	Thank you for your comment. The list of comparators has been amended, rituximab with fludarabine and cyclophosphamide has been replaced with a broader chemoimmunotherapy option. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice.
	UK CLL Forum	The scope is correct to omit Ofatumumab as a comparator. This is not an appropriate single agent therapy in most cases despite being the comparator in the NCT02004522 study. However, venetoclax monotherapy (TA487) should be included as this remains an option in NHS practice in patients where BCRi are contra-indicated or have progressed on a BTKi. Bendamustine monotherapy is very rarely given.	Thank you for your comment. The list of comparators has been amended, rituximab with fludarabine and cyclophosphamide has been replaced with a broader chemoimmunotherapy option. The appraisal committee will discuss the most appropriate

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		Overall, for the purposes of this Draft Scope Ibrutinib or Venetoclax-Rituximab are the most appropriate comparators. Idelalisib-Rituximab is now less often given in UK but we agree that this is a further comparator population. In patients with no TP53 alteration, if patients have not been on a clinical trial (please see 'Population' section), at least one line of chemoimunotherapy will have been given followed by either (2020) single agent Ibrutinib or Venetoclax-Rituximab or less likely continuous Venetoclax monotherapy. Some patients will be eligible for FCR as second line but this is becoming rare and very unlikely to be third line. FCR therefore should not be considered an appropriate comparator. Bendamustine Rituximab in the absence of TP53 alteration could be a useful alternative in a small number of patients and should remain as a comparator. Idelalisib with Rituximab remains a viable if unlikely comparator in cases of relapse within 24 months in the absence of any alternative. Patients with TP53 alteration have more limited options, not being appropriate for chemo-immunotherapy. These patients also generally have shorter PFS after any types of therapy: Comparators include Venetoclax with Rituximab, Ibrutinib, Idelalisib Rituximab and Venetoclax Monotherapy	comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice. Venetoclax monotherapy (TA487) was recommended as a treatment option in the Cancer Drugs Fund (CDF) and therefore not considered appropriate as a comparator in this appraisal. Please see the NICE position statement on CDF treatments as comparators.
	Secura Bio Limited	Treatment options for relapsed or refractory CLL are limited, particularly for: patients refractory to rituximab; patients with cardiac risk; less mobile patients. All the treatments listed are currently used by the NHS, but there is no standard definition of 'best alternative care' and the choice of treatment depends on clinical opinion, the individual patient profile, earlier	Comment noted. No action needed.

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		treatments and other underlying diseases such as cardiac risk and risk factors such as 17p del / TP53 mut status. Duvelisib will offer an additional treatment option for use in CLL after two previous therapies. It could be used in place of any of these treatment options and so all are appropriate comparators.	
Outcomes	CLL Support and Lymphoma Action	Yes but could also include the achievement of minimal residual disease negativity (U-MRD) as a surrogate marker of treatment effectiveness.	Thank you for your comment. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. No action needed.
	UK CLL Forum	Outcomes are appropriate. The Draft Scope is correct to omit Minimal Residual Disease assessment which is a research outcome and unlikely to apply to PI3K inhibitors.	Comment noted. No action needed.
	Secura Bio Limited	Yes	Comment noted. No action needed.
	UK CLL Forum	Costs should also be considered according to likelihood of continued individual patient productivity. The time horizon should be “sufficiently long” to reflect costs and outcomes – The NCT02004522 study demonstrated a median PFS of 16.4months. For many patients there may not be any “next line” therapy and therefore the time horizon should be cognisant of this.	Thank you for your comment the current guide to the methods of technology appraisal states that for the reference case costs should relate to resources that are under the control of the NHS and personal and social services and that productivity

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			costs should be excluded. The reference case for a submission stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. No action needed.
	Secura Bio Limited	No comment.	Noted.
Equality and Diversity	CLL Support and Lymphoma Action	Several poor prognostic groups for CLL Patients have been identified based on CLL characteristics. These include TP53 mutations, 17P del, un-mutated IgHV and complex karyotype. Age should not be a discriminating factor in any way.	Thank you for your comment. The committee will consider equality and diversity concerns related to people with protected characteristics. All relevant subgroups will also be considered when appraising cost-effectiveness. No action needed
	UK CLL Forum	No anticipated discrimination foreseen	Comment noted. No action needed.
	Secura Bio Limited	No change suggested to scope and remit in this regard. In terms of what evidence should be obtained to enable the Committee to identify and consider such impacts, relapsing CLL patients tend to be	Comment noted. No action needed.

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		older and less mobile and therefore have greater difficulty in attending hospital and doctors' offices than the general population. See comment from Chronic Lymphocytic Leukaemia Support Association in scoping consultation for TA561: "Rituximab is administered by intravenous or subcutaneous infusion. This requires hospital attendance and may inhibit some elderly or less mobile patients from access."	
	Leukaemia Care	This should also include people treated with two prior therapies and people without a 17p deletion or TP53 mutation.	Comment noted. The subgroup population list has been updated to include people with or without a 17p deletion or TP53 mutation.
	UK CLL Forum	There is an overwhelming body of evidence to support the consideration of TP53 alteration (17p deletion or TP53 mutation) as a key biological determinant of treatment response and must be included as this subgroup for whom treatment options are limited. As stated in the 'Population' section,not all patients with TP53 alteration will have a suitable second line option which could potentially rule out Duvelisib if recommended as strictly 3rd line in this subgroup. Duvelisib could be a useful treatment alternative to BTKinhibitors in patients on oral anticoagulants, those with significant cardiac disease, or intolerance to BTKi.	Comment noted. The scope has been updated to include people with or without TP53 alteration as subgroups that will be considered if the evidence allows. NICE are only able to make recommendations for populations included in the marketing authorisation.
	Secura Bio Limited	No additional suggestions	Comment noted. No action needed.

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Innovation	CLL Support and Lymphoma Action	Duvelisib inhibits both the delta and gamma forms of PI3K, whereas idelalisib only targets the delta form. Researchers believe the dual mechanism of inhibition with duvelisib pro-vides greater efficacy compared to idelalisib.	Comment noted. During the development of the appraisal, the committee will consider the degree to which duvelisib is an innovative technology when making its recommendations. No action needed.
	Leukaemia Care	According to our clinical advisors, duvelisib is unlikely to be widely used across all patient population, due to the associated serious adverse events (AE) profile. However, considering the limited treatment options available overall and for patients that have exhausted their options, this treatment may offer an important alternative at that point. Duvelisib has been shown to be an effective treatment option in the phase 3 DUO trial. In terms of significant improvement in progression-free survival (PFS) and overall response rate (ORR) when compared to ofatumumab in the relapsed/refractory settings. However, a very high percentage of patients discontinued treatment, many due to serious AEs. There is evidence to show how dose modification could help manage the AEs and still allow the patient to benefit from the treatment. The side effects profile and whether this would be applicable in standard clinical practice needs to be considered.	Comment noted. During the development of the appraisal, the committee will consider the degree to which duvelisib is an innovative technology when making its recommendations. No action needed.
	UK CLL Forum	Duvelisib has dual activity against two PI3K isoforms gamma and delta. Idelalisib is active against the delta isoform only. This dual activity may confer additional efficacy or reduce frequency of resistance. However this drug is unlikely to be seen by the CLL treating community as a step change in the management of the disease.	Comment noted. During the development of the appraisal, the committee will consider the degree to which duvelisib is an innovative technology

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		There remain cases of unmet need in CLL following BTKi and Venetoclax based therapies.	when making its recommendations. No action needed.
	Secura Bio Limited	Yes, as the only approved dual inhibitor of both PI3K-δ and PI3K-γ, as an oral formulation and used as monotherapy, we do consider duvelisib to be innovative. Duvelisib is taken orally twice per day, meaning that patients are not required to attend the hospital to receive treatment (outside of routine monitoring visits). The ability to take treatment in the community setting allows patients to spend more time with their families, and may allow some patients to return to work. The benefits of taking an oral treatment versus a treatment which requires frequent hospital visits for administration are challenging to capture within utility valuation, and so it is unlikely that this important benefit of duvelisib will be reflected within the calculation of QALYs.	Comment noted. During the development of the appraisal, the committee will consider the degree to which duvelisib is an innovative technology when making its recommendations. No action needed.
	UK CLL Forum	We would wish to see patients who have received treatment on clinical trials such as FLAIR to be considered for treatment given the high percentage of patients with CLL in the UK that are treated on trials	Comment noted. NICE are only able to make recommendations for populations included in the marketing authorisation. No action needed.
	Secura Bio Limited	**Question: Where do you consider duvelisib will fit into the existing NICE pathway, blood and bone marrow cancers** Based on its approved indication and on clinical expert opinion[2], the anticipated position in the CLL treatment pathway for duvelisib is:	Thank you for your comments. No action needed.

[2] England & Wales CLL HCP Advisory Board, held on 17th June 2021

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		• After two prior therapies:
		  ○ as an alternative mechanism of action after a BTKi and a BCL-2i (separately or in combination); or
		  ○ after at least one rituximab-containing regimen; or
		  ○ where one of the above has failed and the others are contra-indicated (e.g. because of cardiac risk);
		• As an oral monotherapy, in preference to idelalisib + rituximab, saving the NHS costs and the patient potential treatment delay arising from challenges in scheduling IV infusion, or where the patient is elderly or otherwise less mobile and the need for hospital or physician office visits ought to be minimised;
		• As an option for bridging therapy between front line treatment and allogeneic stem cell transplant, in transplant-suitable patients.
		
		Question: Do you consider that there will be any barriers to adoption of this technology into practice? No.
		
		Question: Would it be appropriate to use the cost comparison methodology for this topic? No.
		
		Question: Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes.
		
		Question: Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? No.	

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	UK CLL Forum	NCT02004522 excluded patients with prior PI3K or BTKi therapy. Given that resistance mechanisms are unlikely to overlap there may not be any biological reason for bringing that forward as a consideration in this TA.	Comments noted. No change to the scope required.

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

N/A