Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2427

venetoclax 10mg, 50mg, 100mg film-coated tablets (Venclyxto®)

AbbVie Ltd

8 April 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

venetoclax (Venclyxto®) is accepted for restricted use within NHSScotland.

Indication under review: In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)

SMC restriction: in patients without del (17p)/TP53 mutation who are fit to receive fludarabine, cyclophosphamide and rituximab (FCR) chemo-immunotherapy

Venetoclax in combination with obinutuzumab, compared with standard therapies, was associated with clinical benefits in patients who were fit and unfit to receive FCR chemo-immunotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

For SMC advice relating to the use of venetoclax in (1) patients without del (17p)/TP53 mutation who are not fit to receive FCR chemo-immunotherapy and (2) patients with del (17p)/TP53 mutation, please refer to SMC2293.

Chairman
Scottish Medicines Consortium

Published 09 May 2022

Indication

In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).[1]

Dosing Information

Venetoclax 20mg daily for one week, then 50mg daily for one week, then 100mg daily for one week, then 200mg daily for one week, then 400mg daily thereafter. Dosing should commence on day 22 of cycle 1.

Venetoclax is given for a total of twelve 28-day cycles, with the first six cycles in combination with obinutuzumab intravenous (IV) infusion 100mg on day 1 of cycle 1, followed by 900mg which may be administered on day 1 or day 2, then 1,000mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent 28-day cycle, for a total of 6 cycles.

Venetoclax film-coated tablets should be taken with a meal to reduce the risk of lack of efficacy. The tablets should not be chewed, crushed, or broken before swallowing. During the dose-titration phase, venetoclax should be taken in the morning to facilitate laboratory monitoring.

Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.[1]

Product availability date

9 March 2020

Venetoclax meets SMC orphan equivalent criteria in this indication.

Summary of evidence on comparative efficacy

Venetoclax is an inhibitor of B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein that is over-expressed in CLL cells where it mediates tumour cell survival and has been associated with resistance to chemotherapies. Venetoclax has demonstrated cytotoxic activity in tumour cells that overexpress BCL-2.[1] SMC has previously issued advice (SMC2293) for this indication: it is accepted for restricted use within NHS Scotland for use in (1) patients without del (17p)/TP53 mutation who are not fit to receive FCR chemo-immunotherapy and (2) patients with del (17p)/TP53 mutation. The submitting company has requested that venetoclax now be considered when positioned for use in patients without del (17p) or TP53 mutation who are fit to receive fludarabine, cyclophosphamide and rituximab (FCR) chemo-immunotherapy.

An open-label phase III study (CLL14) recruited adults with previously untreated CD20+ CLL and coexisting conditions, with a total score >6 on the Cumulative Illness Rating Scale (CIRS) and/or creatinine clearance (CrCl) <70 mL/min (but not <30mL/min) who required treatment (Binet stage C or symptomatic). Randomisation was stratified by Binet stage (A, B or C) and geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern

Europe; or Latin America). Patients were equally assigned to twelve 28-day cycles of venetoclax orally (commencing on day 22 of cycle 1 with weekly-increasing daily doses of 20mg, 50mg, 100mg, 200mg and then 400mg daily thereafter) or chlorambucil orally at 0.5mg/kg on days 1 and 15 of each cycle. All patients concurrently received obinutuzumab IV (100mg on day 1 and 900mg on day 2 [or 1,000mg on day 1], 1,000mg on day 8 and 1,000mg on day 15 of cycle 1, then 1,000mg on day 1 of cycles 2 through 6). The primary outcome, investigator-assessed progression-free survival (PFS), defined as time from randomisation to the first occurrence of progression or relapse using International Workshop on CLL (iwCLL) 2008 guidelines or death from any cause. This was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients.[2,3]

At the interim analysis (data cut-off August 2018), after a median follow-up of 28.1 months, venetoclax-obinutuzumab compared with chlorambucil-obinutuzumab significantly prolonged PFS as detailed in Table 1. As this crossed the pre-specified early stopping boundary, it became the primary analysis of PFS.[2,3] Updated analyses (data cut-off August 2019 and September 2020) after median follow-up of 39.6 months and 52.4 months, respectively, had similar results.[2,4,5]

Table 1: Investigator-assessed progression-free survival (PFS) in CLL14 study.[2-7]

	August 2018 (primary analysis)		**August 2019**		**September 2020**	
	V-O	**C-O**	**V-O**	**C-O**	**V-O**	**C-O**
	N=216	**N=216**	**N=216**	**N=216**	**N=216**	**N=216**
Events	30	77	42	113	61	138
HR (95% CI), p-value	0.35 (0.23 to 0.53), p<0.001		0.31 (0.22 to 0.44),		0.33 (0.25 to 0.45),	
Median* (months)	NE	NE	NE	35.6	NE	36.4
2-year PFS rate*	88%	64%	88%	65%		
3-year PFS rate*			82%	50%		
4-year PFS rate*					74%	35%

Abbreviations: V = venetoclax, O = obinutuzumab; C = chlorambucil; CI = confidence interval; HR = hazard ratio; NE = not evaluable; PFS = progression-free survival; * estimates from Kaplan-Meier analysis.

Secondary outcomes were assessed at the primary analysis of PFS (August 2018 cut-off) in the hierarchical order listed in Table 2. All were significantly improved with venetoclax-obinutuzumab versus chlorambucil-obinutuzumab, except overall survival, for which data were immature.[2,3]

Table 2: Secondary outcomes of CLL14 at data cut-off August 2018.[2,3]

Outcome#	**Venetoclax-obinutuzumab**	**Chlorambucil-obinutuzumab**	**Treatment effect* (95% CI)**
	N=216	**N=216**	
PFS by IRC	29	79	0.33 (0.22, 0.51)
uMRD bone marrow	123 (57%)	37 (17%)	40% (31, 48)
Complete response	107 (50%)	50 (23%)	26% (17, 35)
uMRD peripheral blood	163 (76%)	76 (35%)	40% (31, 49)
uMRD bone marrow in CR	73 (34%)	23 (11%)	23% (15, 31)

uMRD peripheral blood in CR	91 (42%)	31 (14%)	28% (19, 36)
Overall response	183 (85%)	154 (71%)	13% (5.5, 21)
Overall survival	20	17	1.24 (0.64, 2.40)

Abbreviations: PFS = progression-free survival; IRC = independent review committee assessed; overall response = investigator-assessed complete response [CR], complete response with incomplete bone marrow recovery [CRi] or partial response [PR] on iwCLL 2008 guidelines; complete response = investigator-assessed CR or CRi; uMRD = undetectable minimal residual disease assessed 3 months after completion of treatment (defined as less than one cell in 10,000 leukocytes measured by allele-specific oligonucleotide polymerase chain reaction); # PFS and overall survival outcomes are expressed as number of events, all other outcomes are expressed as responders (%); * Treatment effect expressed as difference in event rates, except for PFS and overall survival, which are expressed as hazard ratios.

Health Related Quality of Life (HRQoL) was assessed using MD Anderson Symptom Inventory (MDASI), European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Quality of Life 5 Dimensions 3 Level version (EQ-5D-3L). These did not show a difference between treatments.[2]

Supportive data was provided by recently published interim results of an open-label phase III study (CLL13), which recruited treatment-naïve, fit (CIRS ≤6) adults with CLL who did not have del(17p) or TP53 mutations. There were 926 patients randomised equally to (1) six cycles of standard chemo-immunotherapy (that is, FCR for patients ≤65 years and bendamustine-rituximab for patients >65 years), (2) venentoclax-obinutuzumab, (3) venetoclax-obinutuzumab-ibrutinib, or (4) venetoclax-rituxumab. The co-primary outcomes are PFS (with results expected in 2023) and undetectable minimal residual disease (uMRD) in peripheral blood at 15 months. Results for the latter at data cut-off 28 February 2021 (median follow-up 27.9 months) indicated that the proportion of patients achieving uMRD in peripheral blood at months 15 was significantly lower with standard chemo-immunotherapy (FCR or bendamustine-rituximab) compared with venetoclax-obinutuzumab and with venetoclax-obinutuzumab-ibrutinib: 52% versus 87% and 92%, respectively, but not compared with venetoclax-rituximab, 57%. At 15 months, overall response rates (complete response [CR], CR with incomplete bone marrow recovery [CRi] and partial response [PR]) in the respective groups was 81%, 96%, 94% and 93%. In the standard chemo-immunotherapy group 66% (150/229) of patients had FCR.[8,9]

The submitting company presented a Bayesian network meta-analysis that compared venetoclax-obinutuzumab with FCR using data from nine studies in treatment-naïve patients with CLL: seven studies in those who were not fit to receive FCR and two studies in patients fit to receive FCR. These network meta-analyses suggested that venetoclax-obinutuzumab, compared with FCR, was likely associated with greater PFS and at least comparable overall survival.

*Other data were also assessed but remain commercially confidential**

Summary of evidence on comparative safety

The regulatory review concluded that there were no new safety concerns for venetoclax identified in CLL14. Venetoclax-obinutuzumab was considered not less toxic than chlorambucil-obinutuzumab. Neutropenia, leading to severe infections, was the key issue in the safety profile of venetoclax-obinutuzumab.[2]

In the CLL14 study at the first analysis (data cut-off August 2018) all patients had completed treatment and the median time since completion of treatment was 17.1 months. Within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups 94% (200/212) and 99% (213/214) patients reported an adverse event, which were related to treatment in 90% and 94% of patients and were of grade 3 or 4 severity in 79% and 77% of patients, respectively. Serious adverse events were reported by 49% and 42%, respectively, and were treatment-related in 26% of patients in both groups. In the respective groups adverse events with a fatal outcome occurred in 16 (7.5%) and eight (3.7%) of patients.[2,7]

In CLL14 (August 2018 cut-off), within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups 16% (34/212) and 15% (33/214) had an adverse event leading to withdrawal of any study treatment and 74% and 68% had a dose interruption, respectively.[2]

In CLL14 (August 2018 cut-off), within the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups, haematological adverse events were reported by 68% and 64%, including neutropenia (58% and 57%), thrombocytopenia (24% and 23%) and anaemia (16% and 19%). Gastrointestinal adverse events were reported by 42% and 35%, including diarrhoea (28% and 15%), nausea (19% and 22%) and constipation (13% and 8.9%). Other common adverse events included pyrexia (23% and 15%), fatigue (15% and 14%), cough (16% and 12%) and headache (11% and 9.8%). Infusion-related reactions (with obinutuzumab) were reported by 45% and 51% of patients, respectively.[2,3]

Adverse events of infections of at least grade 3 severity occurred in 19% and 16% of patients in the respective groups, with pneumonia the most common (4.2% in both groups). Sepsis was reported by more patients in the venetoclax-obinutuzumab group than in the chlorambucil-obinutuzumab group: seven (3.3%) versus two (0.9%) patients.[2,10]

Adverse events with a fatal outcome occurred in 16 (7.5%) and eight (3.7%) patients at the August 2018 cut-off in the venetoclax-obinutuzumab and chlorambucil-obinutuzumab groups, respectively. The most frequently reported adverse event leading to death was sepsis: five patients (2.4%) and one patient (0.5%) in the respective groups. Cardiac arrest was reported in one patient in each group.[2]

*Other data were also assessed but remain commercially confidential**

Summary of clinical effectiveness issues

The treatment landscape for first-line therapy in CLL is evolving. In patients with early CLL without symptoms, active surveillance is employed until disease-related symptoms develop. In patients with early CLL and active disease or in patients with advanced CLL, treatment depends upon the presence of TP53 mutations. The British Society for Haematology (BSH) guideline recommends FCR as initial therapy for previously untreated fit patients without TP53 mutations and bendamustine-rituximab as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, more advanced age, concerns with marrow capacity or patient preference.[11] During the pandemic, the COVID-19 National Cancer Medicines Advisory Group

(NCMAG) issued interim advice supporting use of acalabrutinib monotherapy and ibrutinib monotherapy for adults with previously untreated CLL without a del(17p) or TP53 mutation who would otherwise be eligible for FCR.[12] Acalabrutinib and ibrutinib have not been considered as relevant comparators as this COVID-19 NCMAG advice is temporary.

In the CLL14 study, which recruited treatment-naïve adults with CLL and co-morbidities that may prevent use of FCR, venetoclax-obinutuzumab significantly increased PFS compared with a standard of care in this group, chlorambucil-obinutuzumab, with HR of 0.35 (95% CI: 0.23 to 0.53), 0.31 (95% CI: 0.22 to 0.44) and 0.33 (95% CI: 0.25 to 0.45) at the August 2018, August 2019 and September 2020 cut-offs, respectively. Effects on PFS were supported by benefits in response rates and uMRD. Overall survival data remain immature at the latest data cut-off at September 2020. Quality of life measures indicated no difference between the treatment groups.[2-7] Although the CLL14 study did not include patients who were fit to receive FCR, the regulatory review recommended that the licence for venetoclax-obinutuzumab could include these patients as extrapolation of efficacy to younger and more fit patients was considered acceptable. As the safety profile of venetoclax-obinutuzumab in younger and more fit patients was not anticipated to be less favourable than in older patients and the effect size (although not directly compared with FCR) was considered sufficient to make it a reasonable first-line treatment alternative, where the differential safety profile compared to chemotherapy is notable.[2]

The CLL14 study did not provide evidence in patients representative of the proposed positioning, that is, treatment-naïve patients without del(17p) or TP53 mutation who were fit to received FCR. However, this group of patients was included in the CLL13 study, for which interim results have recently been published. These indicate that rates of uMRD at month 15 were significantly greater with venetoclax-obinutuzumab compared with standard chemo-immunotherapy (FCR for those ≤65 years and bendamustine-rituximab for those >65 years): 86% versus 52%.[9] This provides reassurance that outcomes with venetoclax-obinutuzumab maybe similar or better than those with FCR. However, it is not possible to quantify relative efficacy from these data, which do not include a subgroup analysis in those who received FCR.

Within the submission there was an indirect comparison of venetoclax-obinutuzumab versus FCR. It was limited by substantial heterogeneity between the two FCR studies and the other seven studies in the network. The two FCR studies included populations that were generally younger and fitter than the other studies. The other seven studies included patients who were not fit for FCR and, therefore, not representative of the proposed positioning. Direct and indirect estimates indicated inconsistency within the network and the proportional hazards assumption within the included studies had not been tested. There was some heterogeneity in duration of follow-up. Due to these limitations, the results are uncertain.

Although there was no cross-over permitted between treatment groups in the CLL14 study, some patients in the chlorambucil-obinutuzumab group have received venetoclax-obinutuzumab after disease progression. It is possible that between-group differences in post-progression anti-lymphoma treatments may confound overall survival results.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of venetoclax-obinutuzumab for the treatment of adult patients with previously untreated CLL. The base case analysis used FCR as the comparator for the non-del(17p)/TP53 mutation population suitable for FCR chemotherapy.

A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states: pre-progression (starting health state), post-progression and death. The cycle length was 28 days, with patients either remaining in state, transitioning to post-progression or death at the end of each cycle. An NHS perspective and a 30-year time horizon were selected in the base case of the economic model.

There was no direct clinical evidence available for venetoclax-obinutuzumab versus FCR, hence clinical evidence informing the base case analysis was taken from a network meta-analyses (NMA) that compared venetoclax-obinutuzumab with FCR for the treatment of adult patients with previously untreated CLL without del(17p) or TP53 mutation. As indicated above, one of the limitations of the NMA is the inclusion of patients who are suitable and unsuitable to receive FCR immuno-chemotherapy. Using the network, hazard ratios with credible intervals were calculated for FCR with respect to PFS and overall survival using venetoclax-obinutuzumab as a reference. The mean hazard ratios and extrapolated PFS and overall survival curves were utilised in the economic model along with time-to-next-treatment (TTNT) and time-on-treatment as secondary outcomes. The previous submission (SMC2293) informed baseline patient characteristics and base case parameter distribution choices, however where appropriate external literature sources were also used to do the same for the FCR arm.

Base case utilities were obtained from a past National Institute of Health and Care Excellence (NICE) technology appraisal 343 (TA343).[13] These are outlined in Table 3. Utility values elicited from the CLL14 study were considered implausibly high and were not used in the base case analysis.

Table 3: Base case utility values

Health state	Base case utility value
Pre-progression while on IV treatment	0.670
Pre-progression off-treatment	0.760
Pre-progression oral treatment	0.710
Post-progression	0.600

Acquisition and administration costs for venetoclax-obinutuzumab and FCR were included in the analysis, as were the costs associated with any subsequent treatments. Unit costs for managing adverse events, disease management, and a one-off cost for terminal care were also included.

The base case analysis presented by the submitting company found venetoclax-obinutuzumab to be dominant over FCR, meaning that venetoclax-obinutuzumab was associated with higher average quality-adjusted life-years (QALYs) and lower costs versus FCR in the non-del(17p)/TP53

population suitable for FCR. Venetoclax-obinutuzumab produced an incremental QALY gain of 1.748. Although an incremental LY gain can be observed in the results, the model did not assume any difference in OS gain between venetoclax-obinutuzumab and FCR and so, the resulting gain is driven by difference in PFS and subsequent treatments.

A simple Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount is offered on the list price of the medicine.

The results presented do not take account of the PAS for obinutuzumab, ibrutinib or the PAS for venetoclax but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for obinutuzumab and ibrutinib due to commercial confidentiality and competition law issues. As such, only the list price results can be presented.

Table 4: Base case cost-effectiveness results at list price for venetoclax-obinutuzumab versus FCR (deterministic)

Treatment	Total LYG	Total QALYs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
FCR	10.726	5.420			
VenG	13.690	7.168	2.964	1.748	VenG is dominant

Abbreviations: FCR: fludarabine, cyclophosphamide and rituximab; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; VenG: venetoclax with obinutuzumab

The company provided deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario analysis. The DSA showed that the greatest impact on incremental costs and QALYs was the hazard ratio for overall survival followed by the hazard ratio for PFS and PFS utility after initial treatment is completed respectively. These subsequently also act as the key driver for the ICER.

The PSA comprised of a 1000 simulations and provided the probabilities of venetoclax-obinutuzumab being cost-effective at £30K per QALY. The probabilistic results are broadly in line with the deterministic results, with total cost and QALY estimates comparable between the deterministic and the probabilistic analyses, showing that the model is relatively stable when tested for uncertainty and that venetoclax-obinutuzumab is dominant versus FCR. The PSA also indicated a 100% probability of venetoclax-obinutuzumab being cost-effective versus FCR at list price. The results of selected scenario analyses are in the Table 5 below.

Table 5: Selected scenario analysis venetoclax-obinutuzumab versus FCR- list price

	Scenario	Incremental QALYs	Incremental LY	ICER
0	**Base case**	**1.748**	**2.964**	**Dominant**
1	Discount rate. Costs: 0%, QALYs: 0%	2.619	2.964	Dominant
2	Time horizon: 10 year	0.764	0.769	Dominant

3	TLS prophylaxis costs applied to VenG only	1.748	2.964	Dominant

4	Utility (from CLL14 trial) Pre-progression utility = 0.822	2.092	2.964	Dominant
5	Post-progression survival from CLL11	1.892	3.119	Dominant
6	Subsequent treatment mix: 100% ibutrinib (both arms)	1.748	2.964	Dominant
7	Subsequent treatment mix: 100% ibutrinib for VenG arm, 50% ibrutibib and 50% VenR for FCR arm	1.748	2.964	Dominant
8	Subsequent treatment mix: 100% ibutrinib for VenG arm, 80% ibrutinib and 20% VenR for FCR arm	1.748	2.964	Dominant
9	Subsequent treatment mix: 20% ibutrinib and 80% VenR for VenG arm, 80% ibrutinib and 20% VenR for FCR arm	1.748	2.964	Dominant
10	90% excess risk added to background mortality	1.545	2.402	Dominant
11	OS distribution- best statistical fit (Log-normal)	1.741	2.950	Dominant
12	PFS -Independent Model Weibull	1.712	2.964	Dominant
13	PFS -Independent Model- best statistical fit Gompertz	1.357	2.964	Dominant
14	PFS -Dependent Model Weibull	1.516	2.964	Dominant
15	Extreme scenario –most conservative PFS, OS distribution	1.408	2.261	Dominant

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life year; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life-year; VenG: venetoclax with obinutuzumab; FCR: fludarabine, cyclophosphamide and rituximab; VenR: venetoclax with rituximab; TLS: tumour lysis syndrome.

There were a number of limitations with the analysis which include the following:

- No direct evidence about the long-term relative effectiveness of venetoclax-obinutuzumab versus FCR for non-del(17p)/TP53 population suitable for FCR is available. The NMA used to obtain mean hazard ratios for FCR versus venetoclax-obinutuzumab is limited by the fact that it also included trials with patients unsuitable to receive FCR, which is not representative of the positioning. This raises some uncertainty around the relative efficacy and safety of venetoclax-obinutuzumab versus FCR.

- The CLL14 study data for venetoclax-obinutuzumab is immature and due to the absence of mature study data, there is uncertainty around the treatment effect on overall survival and therefore, further uncertainty around the extrapolated overall survival. The extrapolated overall survival was found to be close to the level of background mortality, and given that CLL patients tend be older, the likelihood of death from all-cause mortality is high. Hence, the base case analysis assumed that first-line treatment does not have an effect on overall survival. However, the effect of using alternative distributions for the overall survival dependent survival model (assuming either no treatment effect or treatment effect) does not lead to large changes in incremental results. Hence overall, results consistently

demonstrated that venetoclax-obinutuzumab is dominant versus FCR across different models and distributions selection.

- The base case analysis found treatment with venetoclax-obinutuzumab to be associated with lower total costs compared with FCR due to substantially lower subsequent treatment costs in the non-del(17p)/TP53 population suitable for FCR. Accrued costs were lower due to the superior PFS achieved by patients on venetoclax-obinutuzumab, which delays initiation of potential second-line treatment. The modelling of subsequent treatment costs was contingent on the type of subsequent treatment mix received, the TTNT curves, and duration of second-line treatment. There is some uncertainty about the extrapolation of TTNT due to the lack of mature study data as well as potential variation in the types of subsequent treatment mix. It is therefore unclear whether the very large cost savings predicted would be achieved in reality.
- Base case utilities were obtained from a past NICE appraisal TA343 – chlorambucil-obinutuzumab for untreated CLL.[13] These were preferred to the utility values elicited from the CLL14 study which were notably higher than those used in previous appraisals and also higher than UK-age adjusted general population values. The post-progression utility values from CLL14 were also unreliable due to the low number of patients progressing during the trial period. The impact of applying higher CLL14 based utility values was tested in the scenario analysis, but did not alter the conclusion of venetoclax-obinutuzumab dominance.

Despite the uncertainties, venetoclax-obinutuzumab remained dominant in all scenarios. Therefore, the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a joint patient group submission from Leukaemia Care, CLL support and Lymphoma Action. All three organisations are registered charities.

- Leukaemia Care has received 14.3% pharmaceutical company funding in the past two years, including from the submitting company. CLL Support has received 58.8% pharmaceutical company funding in the past two years, including from the submitting company. Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, including from the submitting company.

- Living with CLL has a significant physical, psychological and financial impact on patients and their family/friends, which affects their quality of life. Common symptoms include fatigue, swollen lymph nodes and fever or night sweats. Patients with CLL also have a higher risk of infection. These frequent and persistent infections can impact hugely on quality of life, as well as being a leading cause of death for CLL patients. There is also a financial impact of living with CLL, due to time taken off work, reducing work hours or retiring and increased costs of travel to appointments, parking costs etc.

- The current standard of care option for many with CLL is the chemo-immunotherapy FCR, which comes with many side effects and potentially long-term side effects including a risk of secondary cancers.

- Venetoclax with obinutuzumab is a treatment of a limited duration, offering durable remissions and a treatment free period; these are seen as favourable attributes of treatment options by patients. In comparison with FCR, venetoclax with obinutuzumab also has more tolerable side effects, which typically allows patients to live a more "normal" life, therefore giving this treatment great potential to improve many patient's quality of life and experience of care.

Additional information: guidelines and protocols

In 2018, the British Society for Haematology (BSH) published a 'Guideline on the treatment of chronic lymphocytic leukaemia'. This recommends FCR as initial therapy for previously untreated fit patients without TP53 mutations and bendamustine plus rituximab as an acceptable alternative for fit patients in whom FCR is contra-indicated due to specific comorbid conditions, more advanced age, concerns with marrow capacity or patient preference. In less fit patients chlorambucil-obinutuzumab is recommended and bendamustine-rituximab might be considered as an alternative. Also, ibrutinib is an acceptable treatment option. Chlorambucil in combination with rituximab is not routinely recommended. In extremely frail patients single agent chlorambucil may be used in those who are intolerant of anti-CD20 antibodies or when intravenous therapy is considered unsuitable, corticosteroid monotherapy can be considered, but rituximab monotherapy is not recommended. In patients with TP53 mutation, ibrutinib is the treatment of choice. Idelalisib-rituximab is a suitable alternative for patients for whom ibrutinib is deemed inappropriate.[11]

In 2020, the European Society of Medical Oncology (ESMO) published a 'Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up'. This recommends FCR or ibrutinib as front-line therapy for fit patients without del(17p) or TP53 mutations. It also notes that venetoclax plus obinutuzumab might be an alternative to Bruton tyrosine kinase inhibitors (BTKis), but data for fit patients are still pending.[14]

Additional information: comparators

In patients without del(17p)/ or TP53 mutation who are fit to receive FCR, it is the comparator.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Venetoclax Obinutuzumab	From day 22 of cycle 1 a daily oral dose of 20mg increasing at weekly intervals to 50mg, 100mg, 200mg, then continuing at 400mg daily to the end of twelve 28-day cycles. Intravenous infusion of 100mg on day 1 of Cycle 1, followed by 900mg (on day 1 or 2), then 1,000mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent 28-day cycle, for six cycles.	76,696

Costs from BNF online on 21 January 2022. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

References

1. Abbvie. Venetoclax 10mg, 50mg, 100mg film-coated tablets (Venclyxto®) summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/. Last updated 21/04/20.

2. European Medicines Agency. European public assessment report Committee for Medicinal Products for Human Use (CHMP) group of variations including an extension of indication assessment report: venetoclax (Venclyxto®), EMA/166265/2020, 30 January 2020.

3. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med 2019; 380: 2225-2236.

4. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020; 21: 1188-1200.

5. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. J Clin Oncol 2021; 39: 4049-60.

6. F. Hoffmann-La Roche Ltd, AbbVie Inc. Supplement to Clinical Study Report 1088081 GDC-0199/ABT-199/Protocol BO25323.

7. F. Hoffmann-La Roche Ltd, AbbVie Inc. Supplement #2 to Clinical Study Report 1088081 GDC-0199/ABT-199/Protocol BO25323.

8. Clinicaltrials.gov. Record for NCT02950051. Accessed on 20/01/22.

9. Eichhorst B, Niemann C, Kater AP, et al. A randomized phase III study of venetoclax-based time-limited combination treatments (RVe, GVe, GIVe) vs standard chemoimmunotherapy (CIT: FCR/BR) in frontline chronic lymphocytic leukemai (CLL) of fit patients: first co-primary endpoint analysis of the international intergroup GAIA (CLL13) trial. Blood (2021) 138 (Supplement 1): 71

10. F. Hoffmann-La Roche Ltd. Primary clinical study report: BO25323 (CLL14).

11. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. British Journal of Haematology, 2018, 182, 344–359.

12. Scottish Government. Coronavirus (COVID-19): Interim cancer treatment options. Last updated 28 October 2021. Available at https://www.gov.scot/publications/coronavirus-covid-19-interim-cancer-treatment-options/

13. National Institute for Health and Care Excellence (NICE). Technology appraisal 343 (TA343): Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia, 2 June 2015. https://www.nice.org.uk/Guidance/TA343.

14. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021: 32: 23-33.

This assessment is based on data submitted by the applicant company up to and including 11 March 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.