# Horizon Scanning in Oncology

## Venetoclax (Venclexta™) for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with chromosome 17p deletion

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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# 1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to predefined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

**EUnetHTA HTA Core Model®**

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| **Description of the technology** | |
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# 2 Drug description

## Generic/Brand name/ATC code:

Venetoclax/Venclexta™/L01XX52

### B0001: What is venetoclax?

BCL-2 specific, small-molecule inhibitor

Venetoclax is an oral, selective, small-molecule inhibitor of the pro-survival B-cell lymphoma 2 (BCL-2) proteins [2-4]. Overexpression of BCL-2 can cause increased apoptosis resistance and prolonged survival of chronic lymphocytic leukaemia (CLL) B-cells [5]. Venetoclax binds the BCL-2 protein directly, displaces pro-apoptotic proteins like BIM (BCL-2-like protein 11), triggers mitochondrial outer membrane permeabilisation and activates caspases. These processes help to restore the apoptotic ability of malignant cells [3, 4].

once daily 400 mg after a weekly dose ramp-up schedule

The recommended daily dose of venetoclax is 400 mg until disease progression or unacceptable toxicity is observed. The initial daily dose starts at 20 mg for 7 days, followed by a weekly ramp-up dosing schedule over 5 weeks until 400 mg have been reached. This should gradually reduce tumour burden as well as decrease the risk of tumour lysis syndrome. Venetoclax tablets should be administered daily with a meal and water at about the same time [3].

### A0022: Who manufactures venetoclax?

AbbVie Inc. & Genentech USA, Inc.

# 3 Indication

### A0007: What is the target population in this assessment?

indicated for relapsed/refractory del(17p) CLL

Venetoclax (Venclexta™) is indicated for the treatment of relapsed or refractory CLL patients with chromosome 17p deletion (del[17p]), who have received at least one prior therapy.

# 4 Current regulatory status

**A0020: For which indications has venetoclax received marketing authorisation?**

FDA approval for CLL since 2016

In April 2016, the US Food and Drug Administration (FDA) approved venetoclax for the treatment of CLL patients with del(17p), as determined by an FDA-approved test (Vysis CLL FISH probe kit, Abbott-Molecular, Des Plaines, IL, USA), and who have received at least one prior therapy. Venetoclax has been approved under accelerated approval and received orphan status based on the interim analysis of a single-arm phase II study (M13-982) [3].

venetoclax received orphan designation by the EMA

Venetoclax has not yet been approved by the European Medicines Agency (EMA), but it received orphan designation in February 2016 for the treatment of acute myeloid leukaemia patients who are older than 65 years and who cannot receive standard treatment. Confirmation of a significant benefit for this patient group is needed at the time of marketing authorisation to retain the orphan status [6].

# 5 Burden of disease

**A0002: What is CLL?**

lymphoid neoplasm

CLL is a B-cell chronic lymphoproliferative disorder (lymphoid neoplasm) that pertains to the B-cell non-Hodgkin lymphomas (NHL) [7]. It is characterised by the clonal proliferation as well as the accumulation of mature, functionally incompetent and typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen [7-9].

**A0004: What is the natural course of CLL?**

highly variable courses of disease

Typically, CLL is characterised by a highly variable course of disease, whereby the majority of patients will have an indolent (slow-growing) disease [7, 9, 10]. Other patients die rapidly (2–3 years) after diagnosis due to complications or causes directly related to CLL, whereas others live for 5 to 10 years with an initial course of disease followed by a terminal course for 1–2 years. The major causes of death are systematic infections (e.g. pneumonia and septicaemia), bleeding and inanition with cachexia [7].

**A0006: What are the consequences of CLL for the society?**

**A0023: How many people belong to the target population?**

NHL incidence rate in Austria 9.0 per 100,000 persons/year

CLL is the most frequent type of leukaemia in western countries [9, 11]. In Austria, the incidence of NHL is 9.0 per 100,000 persons per year (2012); in 2012, more than 1,200 persons were newly diagnosed. About 60% of all newly diagnosed NHLs were B-cell lymphomas [12]. CLL is most commonly di-

median age at diagnosis: 71

agnosed among people aged between 65 and 74 years; the median age at diagnosis is about 71 years [13]. 5–10% of CLL patients have a detectable del(17p) or a mutation of the p53 gene [14]. In Austria, men have 1.4 times higher incidence and 1.8 times higher mortality rates than women [12].

### A0005: What are the symptoms and the burden of CLL?

usually CLL does not cause any signs or symptoms

Typically, CLL patients do not show any signs or symptoms. However, if symptoms or signs are present they can occur in a wide range, like painless swelling of the lymph nodes (e.g. cervical area, neck and stomach), pain below the ribs, tiredness, lymphadenopathy, splenomegaly and hepatomegaly [11, 15]. Nevertheless, only 5–10% of CLL patients show one or more of the so called "B symptoms", which include unintentional weight loss, fevers and night sweats without evidence of infection, and extreme fatigue [11].

### A0003: What are the known risk factors for CLL?

associated risk factors: gender, ethnicity, age and family history

Predisposition to CLL due to occupational or environmental risks is not definitively discernible [11]. Risk factors associated with CLL are a family history of CLL or other lymph-related cancers, older age, gender (men are more often affected than women) and ethnicity [9, 16].

### A0024: How is CLL currently diagnosed according to published guidelines and in practice?

often diagnosed via routine blood count tests

The diagnosis of CLL is established via blood counts, blood smears, and immunophenotyping of circulating B-lymphocytes ($\geq 5 \times 10^9$/L) [9, 17]. However, often CLL is diagnosed during routine blood count tests that reveal an absolute lymphocytosis [11]. An additional computed tomography (CT) may be performed in patients suspected of having enlarged abdominal or pelvic nodes [7].

two staging systems: Binet and Rai

CLL patients are prognostically grouped following the Rai and the Binet staging systems, based on physical examination and complete blood counts [7, 9, 10]. The Rai staging system is based on the idea that CLL is a gradual and progressive increase in the body burden of leukaemic lymphocytes starting from lymphocytosis. It consists of the following three groups [7]:

- Stage 0 (low risk): lymphocytosis
- Stages I to II (intermediate risk): lymphadenopathy, organomegaly
- Stages III to IV (high risk): anaemia, thrombocytopenia.

Binet staging system is based on the number of involved sites

In contrast, the Binet staging system takes five potential areas of involvement into consideration: cervical, axillary, inguinal lymph nodes, spleen and liver. The classification of patients is based on the number of involved sites as well as the presence of anaemia and/or thrombocytopenia [7, 9]:

- Stage A: fewer than three involved lymphoid sites
- Stage B: at least three involved lymphoid sites
- Stage C: existence of anaemia and/or thrombocytopenia.

Additionally, lymphocyte doubling time, beta-2 microglobulin, and genetic abnormalities can be further prognostic factors [7].

# 6 Current treatment

**A0025: How is CLL currently managed according to published guidelines and in practice?**

observation in asymptomatic CLL patients

Immediate treatment is indicated in CLL patients that show an active disease which is manifested by advanced stage, high tumour burden, severe disease-related "B symptoms" or repeated infections. Otherwise, the majority of early-stage CLL patients are managed initially with watchful waiting. In general, patient fitness, comorbidities as well as the patient's performance status should be determined prior to the initiation of treatment [17, 18]. Currently, the only curative treatment option for CLL patients is allogeneic hematopoietic cell transplantation [18].

1st-line therapy options: chlorambucil-based chemotherapy, FCR, bendamustine + rituximab

Due to differences in patient age and fitness, no uniform front-line regimen is recommended for all symptomatic CLL patients. However, there are several initial treatment options available, like chlorambucil-based chemotherapy, fludarabine, rituximab and cyclophosphamide (FCR) or bendamustine plus rituximab [10, 17, 18].

no agreed standard therapy for relapsed or refractory CLL patients

No standard treatment has yet been established for the treatment of relapsed or refractory CLL patients [10]. However, once a patient is considered to have relapsed or refractory CLL, the diagnosis has to be reconfirmed by a complete blood count with differential flow cytometry of the peripheral blood. In addition, FISH testing should be repeated to determine specific chromosomal deletions. CLL patients with asymptomatic recurrent CLL do not inevitably need instant treatment but should be closely observed [18].

early relapse and del(17p) CLL: clinical trials, ibrutinib, idelalisib + rituximab

late relapse CLL: retreatment with the prior therapy, ibrutinib, alternatively idelalisib + rituximab

Generally, treatment options are dependent on the quality and duration of response to the previous treatment. Therefore, CLL patients who showed an initial response duration that was significantly less than the median for a respective treatment can be considered for another regimen at relapse. For patients with an early relapse (< 6 months) and those with 17p deletion ibrutinib monotherapy could offer a treatment option. If ibrutinib is not tolerated or contraindications exist, idelalisib plus rituximab may be considered. For patients who progress one year after initial therapy (late relapse), retreatment with the prior therapy can be an option as well as ibrutinib monotherapy or idelalisib plus rituximab [9, 17, 19].

# 7 Evidence

literature search in 5 databases: 246 hits

A literature search was conducted on 4 August 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "Venetoclax", "Venclexta", "GDC-0199", "ABT-199", "RG7601", "chronic lymphocytic leukaemia", "chronic lymphocytic leukemia" and "CLL". Also, the manufacturer was contacted, who submitted eight references (three of which had already been identified by systematic literature search). Manual search identified 25 additional references (web documents and journal articles).

Overall, 270 references were identified. Included in this report are:

- 1 phase II study, assessing venetoclax in relapsed or refractory CLL patients harbouring a 17p deletion [20, 21]
- 1 phase I study, assessing venetoclax in patients with relapsed or refractory CLL or small lymphocytic lymphoma [22].

**quality of evidence assessed using a modified Downs and Black instrument**

The methodological quality of the evidence was assessed using a Downs and Black instrument [23] that was modified to include the source of funding for studies. Evidence was assessed based on the reporting of trial characteristics, external and internal validity, and confounding. The form used to assess the study quality is reported in Table 4 (see appendix). Study strengths and limitations were reported in preference to a numeric score and can be found in Table 3 (see appendix).

## 7.1 Clinical efficacy and safety – phase II study

**M13-982: open-label, single-arm phase II study**

M13-982 [20, 21] was an open-label, multicentre, single-arm phase II study assessing the activity and safety of venetoclax monotherapy in patients with relapsed or refractory CLL harbouring a 17p deletion. Reported are the results of a pre-specified interim analysis; 70 (65%) of 107 patients were on treatment at the time of data cut-off (April 2015) and 37 (35%) had discontinued treatment (22 progressed, 9 had adverse events, 2 withdrew consent, 1 was non-compliant and 3 proceeded to allogenic stem cell transplantation).

**107 relapsed/refractory CLL patients**

**daily dose of 400 mg**

A total of 107 patients were enrolled to receive a 400 mg daily dose of venetoclax until disease progression, unacceptable toxic effects or discontinuation for any other reason. A weekly dose ramp-up from a 20 mg starting dosage to the final 400 mg (20, 50, 100, 200, 400 mg) over 4–5 weeks was performed.

**median follow-up duration: 12.1 months**

The median duration of follow-up at the time of data cut-off was 12.1 months, ranging from 10.1 to 14.2 months. The median time from diagnosis of CLL to the first venetoclax dose was 81.7 months (interquartile range [IQR] 41.0–131.5), and from the last prior therapy to the first dose of venetoclax it was 5.4 months (IQR 2.4–16.5). All patients except for one had a del(17p), assessed by a central laboratory with the Vysis fluorescence in-situ hybridisation (FISH) kit. The median proportion of del(17p) cells was 50.3%, ranging from 23.0% to 83.5%.

**median age of 67 years and ECOG performance status of 0–2**

Enrolled patients were at least 18 years or older and had a median age of 67 (ranging from 37 to 85) years. Relapsed/refractory CLL was defined as relapsed or refractory after receiving at least one prior line of therapy (patients had to receive at least two cycles of the respective treatment). The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 3.

**primary outcome: proportion of patients who achieved an overall response**

The primary outcome of M13-982 was activity of venetoclax monotherapy, measured by the proportion of patients who achieved an overall response (defined as partial remission and higher) assessed by an independent review committee (IRC). The analysis of the primary endpoint was pre-planned to be done once 70 patients completed a week 36 assessment. All other analyses

included all 107 patients who received at least one dose of venetoclax (per-protocol population). Secondary outcomes comprised the proportion of patients with complete remission (CR) and partial remission (PR), time to first response (TTR), duration of overall response (DOR), progression-free survival (PFS), overall survival (OS) as well as adverse events (AEs).

### 7.1.1 Clinical efficacy

**D0001: What is the expected beneficial effect of venetoclax on mortality?**

At the time of interim analysis the median OS (17 deaths) had not been reached. The estimated 12-month OS was 86.7% (95% CI 78.6–91.9), assessed by an independent review committee.

median OS had not been reached, estimated 12-month OS: 86.7%

**D0006: How does venetoclax affect progression (or recurrence) of CLL?**

Median PFS (31 events) had not been reached at the time of interim analysis. The estimated 12-month PFS was 72.0% (95% CI 61.8–79.8) per independent review committee assessment. The median time to progression for CLL was 6.3 months (IQR 4.4–9.8). The estimated 12 months' time to progression (TTP) was 77% (95% CI 67–84).

median PFS had not been reached, estimated 12-month PFS: 72.0%

**D0005: How does venetoclax affect symptoms and findings (severity, frequency) of CLL?**

54 (77%) of patients of the pre-specified study population (70 subjects) achieved an overall response (OR). An OR assessed by IRC (OR-IRC), in the per-protocol population (107 subjects), was achieved in 85 (79.4%, CI 70.5–86.6) patients. 79 (74%) patients in the per-protocol population assessed by the investigator (IA) achieved an OR. CR or CR with incomplete blood recovery of blood counts was achieved in 8 (8%) patients assessed by IRC. A PR in the per-protocol population was achieved in 74 (69%, ICR assessed) patients and a nodular partial remission (NPR) in 3 (3%) patients.

OR-IRC: 79%
CR-IRC: 7%
PR-IRC: 69%
NPR-IRC: 3%

**D0011: What is the effect of venetoclax on patients' body functions?**

No evidence was found to answer this research question.

**D0012: What is the effect of venetoclax on generic health-related quality of life?**

No evidence was found to answer this research question.

**D0013: What is the effect of venetoclax on disease-specific quality of life?**

There was no evidence found to answer this research question but patient-reported outcome measures will be investigated in a safety expansion cohort of the M13-982 trial.

QoL data will be investigated in a safety expansion cohort

*Table 1: Efficacy results of trial M13-982*

| | | | |
|---|---|---|---|
| **Descriptive statistics and estimate variability** | Treatment group | | Venetoclax |
| | Number of subjects | | 107 |
| | OR | OR-IRC (n = 70)[1], n (%) | 54 (77) |
| | | OR-IRC, n (%)<br>95% CI | 85 (79)<br>70.5–86.6 |
| | | CR-IRC[2], n (%) | 8 (8) |
| | | PR-IRC, n (%) | 74 (69) |
| | | NPR-IRC, n (%) | 3 (3) |
| | | OR-IA, n (%) | 79 (74) |
| | PFS | Median PFS, months<br>12-month PFS, %<br>95% CI | NR<br>72.0<br>61.8–79.8 |
| | OS | Median OS, months<br>12-month OS, %<br>95% CI | NR<br>86.7<br>78.6–91.9 |

*Abbreviations: CI = confidence interval, CR = complete remission, IA = assessed by an investigator, ICR = assessed by an independent review committee, NPR = nodular partial remission, NR = not reached, OR = overall response, OS = overall survival, PFS = progression-free survival, PR = partial remission*

## 7.1.2 Safety

**C0008: How safe is venetoclax in relation to no intervention?**

**most common grade 3–4 AEs: neutropenia, infection, anaemia, and thrombocytopenia**

As the M13-982 trial was a single-arm study, no results comparing venetoclax to a comparator are available. However, the treatment-related grade 3–4 AEs that occurred most commonly in the per-protocol population were neutropenia (40%), infection (20%), anaemia (18%) and thrombocytopenia (15%). Serious infections that occurred in at least two patients were pneumonia (6%), lower respiratory tract infection (2%) and upper respiratory tract infection (2%). Grade 5 AEs occurred in 12 (11%) patients, of which seven had a malignant neoplasm progression. In total, 18 (17%) patients died in the course of the study, of which seven died due to disease progression, four because of an AE and seven due to progressive disease after 30 days from discontinuation of venetoclax. All treatment-emergent AEs can be found in Table 2.

**C0002: Are the harms related to dosage or frequency of applying venetoclax?**

[1] Pre-planned analysis of overall response that was performed once 70 patients completed a week 36 assessment

[2] Complete remission or complete remission with incomplete recovery of blood counts

**dose reductions due to AEs (neutropenia, infection, etc.)**

In a total of 13 (12%) patients (107 subjects), dose reductions were required owing to AEs. Dose interruptions or reductions, or granulocyte-colony stimulating factor treatment and antibiotics were necessary due to grade 3–4 AE neutropenia. Infections led to an interruption of treatment with venetoclax in 10 (9%) patients and to dose reductions in two (2%) patients. In two (2%) patients, treatment interruptions were also indicated in consequence of tumour lysis syndrome.

### C0005: What are the susceptible patient groups that are more likely to be harmed through the use of venetoclax?

**tumour lysis syndrome and embryo-foetal harm**

In previously treated CLL patients with high tumour burden, hyperuricaemia or chronic kidney disease, the treatment with venetoclax can cause tumour lysis syndrome, including fatal events and renal failure requiring dialysis. Furthermore, venetoclax may cause embryofoetal harm when administered to a pregnant woman. However, there are no adequate and well-controlled studies available investigating venetoclax in pregnant women [3].

*Table 2: Most frequent treatment-related adverse events*[3]

| **Adverse event** (according to NCI-CTC version 4.0) | **Venetoclax** (n = 107) | | | |
|---|---|---|---|---|
| | Grade 1–2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) |
| Any treatment-related AEs | 22 (21) | 37 (35) | 32 (30) | 12 (11) |
| Blood and lymphatic disorders | 8 (8) | 26 (24) | 31 (29) | 0 (0) |
| Anaemia | 10 (9) | 19 (18) | 0 (0) | 0 (0) |
| Autoimmune haemolytic anaemia | 1 (1) | 4 (4) | 3 (3) | 0 (0) |
| Febrile neutropenia | 0 (0) | 4 (4) | 1 (1) | 0 (0) |
| Immune thrombocytopenia purpura | 0 (0) | 1 (1) | 4 (4) | 0 (0) |
| Leukopenia | 0 (0) | 4 (4) | 1 (1) | 0 (0) |
| Neutropenia | 3 (3) | 18 (17) | 25 (23) | 0 (0) |
| Thrombocytopenia | 4 (4) | 4 (4) | 12 (11) | 0 (0) |
| Cardiac disorders | 7 (7) | 4 (4) | 0 (0) | 1 (1) |
| Atrial fibrillation | 4 (4) | 2 (2) | 0 (0) | 0 (0) |
| Cardiopulmonary failure | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Gastrointestinal disorders | 60 (56) | 7 (7) | 0 (0) | 0 (0) |
| Constipation | 11 (10) | 0 (0) | 0 (0) | 0 (0) |
| Diarrhoea | 31 (29) | 0 (0) | 0 (0) | 0 (0) |
| Nausea | 30 (28) | 1 (1) | 0 (0) | 0 (0) |
| Vomiting | 15 (14) | 1 (1) | 0 (0) | 0 (0) |
| General disorders | 54 (51) | 4 (4) | 1 (1) | 1 (1) |
| Disease progression | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Fatigue | 23 (22) | 0 (0) | 0 (0) | 0 (0) |

[3] Reported are grade 1–2 AEs occurring in at least 10% of patients, grade 3–4 AEs in two or more patients and all grade 5 AEs

| | | | | |
|---|---|---|---|---|
| Pyrexia | 20 (19) | 1 (1) | 0 (0) | 0 (0) |
| Hepatobiliary disorders | 2 (2) | 2 (2) | 0 (0) | 1 (1) |
| Hepatic function abnormal | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Hyperbilirubinaemia | 0 (0) | 2 (2) | 0 (0) | 0 (0) |
| Infections and infestations | 56 (52) | 14 (13) | 6 (6) | 1 (1) |
| Lower respiratory tract infection | 4 (4) | 2 (2) | 0 (0) | 0 (0) |
| Nasopharyngitis | 15 (14) | 0 (0) | 0 (0) | 0 (0) |
| *Pneumocystis jirovecii* pneumonia | 0 (0) | 2 (2) | 0 (0) | 0 (0) |
| Pneumonia | 4 (4) | 4 (4) | 1 (1) | 0 (0) |
| Septic shock | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Upper respiratory tract infection | 14 (13) | 0 (0) | 2 (2) | 0 (0) |
| Neoplasms benign, malignant, and unspecified | 5 (5) | 9 (8) | 3 (3) | 7 (7) |
| Malignant neoplasm progression | 1 (1) | 2 (2) | 1 (1) | 7 (7) |
| Squamous cell carcinoma of skin | 2 (2) | 2 (2) | 0 (0) | 0 (0) |
| Nervous system disorders | 28 (26) | 3 (3) | 2 (2) | 1 (1) |
| Headache | 12 (11) | 0 (0) | 0 (0) | 0 (0) |
| Haemorrhagic stroke | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Vascular disorders | 9 (8) | 7 (7) | 0 (0) | 0 (0) |
| Hypertension | 2 (2) | 4 (4) | 0 (0) | 0 (0) |

*Abbreviations: AEs = adverse events, NCI-CTC = National Cancer Institute Common Terminology Criteria for Adverse Events*

## 7.2 Clinical efficacy and safety – further studies

**M12-175: efficacy, safety and pharmacokinetic profile of venetoclax in relapsed/refractory CLL**

A multicentre, non-randomised, open-label, phase I dose-escalation study [22] was conducted to assess the safety, pharmacokinetic profile, and efficacy of venetoclax in patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL). 56 patients were included in a dose-escalation phase: they received active treatment in one of eight dose groups that ranged from 150 to 1,200 mg per day. 60 additional patients were enrolled in an expansion cohort to receive weekly gradual ramp-up in doses as high as 400 mg per day.

**79% of patients showed a response to venetoclax**

In 3 of 56 patients of the dose-escalation cohort, tumour lysis syndrome occurred, leading to one death. After that, doses were adjusted, and no tumour lysis syndrome occurred in any of the 60 patients in the expansion cohort. Further toxic effects included mild diarrhoea (52%), upper respiratory tract infection (48%), nausea (47%), and grade 3–4 neutropenia (41%). No maximum tolerated dose could be identified. 92 (79%) of 116 patients showed a response to venetoclax. A CR was achieved in 20% of patients. A 15-month progression-free survival estimate of 69% was found for 400 mg venetoclax.

# 8 Estimated costs

**A0021: What is the reimbursement status of venetoclax?**

To date, venetoclax is not approved in Europe; therefore, there are no price estimates available for Austria at this point. However, additional costs will incur due to tumour lysis syndrome prophylaxis.

no cost estimates available yet

# 9 Ongoing research

In August 2016, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following 3 ongoing phase III trials are investigating venetoclax in patients with CLL:

3 phase III studies are ongoing, investigating venetoclax in patients with CLL

- **NCT02756611:** An open-label, single-arm, phase IIIb multicentre study evaluating the efficacy of venetoclax (ABT-199) in relapsed/refractory subjects with chronic lymphocytic leukaemia (CLL) including those with the 17p deletion or TP53 mutation or those who have received prior treatment with a B-cell receptor inhibitor. Estimated study completion date is August 2020.
- **NCT02005471:** A multicentre, phase III, open-label randomised study in relapsed/refractory patients with chronic lymphocytic leukaemia to evaluate the benefit of GDC-0199 (ABT-199) plus rituximab compared with bendamustine plus rituximab. Estimated study completion date is September 2020.
- **NCT02242942:** An open-label, multicentre, randomised phase III study is designed to compare the efficacy and safety of a combined regimen of obinutuzumab and GDC-0199 versus obinutuzumab + chlorambucil (GClb) in patients with chronic lymphocytic leukaemia (CLL) and coexisting medical conditions. Estimated study completion date is November 2018.

Various phase I and II studies are currently ongoing in different treatment lines and regimens in patients with CLL (e.g. NCT02427451, NCT02756897, NCT01328626, NCT01682616, NCT02141282 and NCT01685892). In addition, venetoclax is also currently investigated for other indications, like multiple myeloma, acute myelogenous leukaemia, diffuse large B-cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma and follicular lymphoma.

numerous ongoing phase I and II trials in different treatment lines and regimens

# 10 Discussion

indication approved by the FDA, but not by the EMA

Since April 2016, venetoclax has been approved by the FDA for the treatment of CLL patients with 17p deletion, as determined by an FDA-approved test (Vysis CLL FISH probe kit), who have received at least one prior therapy [3]. In Europe, venetoclax has not yet received marketing authorisation but it received orphan designation for the treatment of acute myeloid leukaemia in February 2016 [6].

M13-982: OR-IRC was achieved in 85 patients

The FDA approval was based on a multicentre, open-label, single-arm phase II study, the M13-982 trial [20, 21]. The study was conducted to assess the activity and safety of venetoclax monotherapy in 107 patients with relapsed or refractory CLL harbouring a 17p deletion. An OR-IRC was achieved in 85 (79.4%) patients at a median follow-up of 12.1 months. 8% of patients showed a CR-IRC. Neither median OS, median PFS nor median DOR had not been reached at the time of analysis. In general, the prognosis of patients with del(17p) is poor [24, 25]. However, poor-risk cytokinetics like del(17p) were also associated with a shorter duration of response in former studies [25, 26]. This fact highlights the requirement for mature efficacy data.

shorter duration of response in patients with del(17p) → mature data is needed

age was not representative of the actual patient population

Since 46 (43%) patients were under 65 years and CLL is most commonly diagnosed among people aged between 65 and 74, the study population reflected younger patients than are common in clinical practice. In addition, an extensive efficacy and safety profile for patients harbouring an IGVH mutation is necessary due to the small sample size (7 patients) of this subgroup and to exclude any disadvantages, as this patient group achieved a 15% less 12-month PFS estimate compared to the overall population.

most frequent grade 3–4 AEs: neutropenia, infection, anaemia, thrombocytopenia

QoL results are lacking

In regard to safety outcomes, 65% of the per-protocol population experienced treatment-related grade 3–4 AEs (most frequent: neutropenia, infection, anaemia, and thrombocytopenia), another 11% of patients had grade 5 AEs and 17% of patients had died in the course of the study. No patient-reported outcomes, like quality of life (QoL), were available. These measures will be examined in a safety expansion cohort of the M13-982 trial. Those results should be taken into consideration and also set into relation to the final efficacy and safety results.

prophylaxis of tumour lysis syndrome

In former studies, venetoclax has shown an increased risk of tumour lysis syndrome via the rapid reduction of tumour cells [22]. Therefore, prophylaxis and management have been implemented in the M13-982 trial. As a result, tumour lysis syndrome occurred in only five patients. However, once venetoclax is available in Europe, it will be of high importance to introduce this prophylaxis into clinical practice and take its additional costs into consideration.

small sample size of patients who were previously treated with kinase inhibitors

There is currently no appropriate treatment option defined for CLL patients with del(17p), but they are at high risk of either not responding to initial treatment with chemo-immunotherapy or relapsing rapidly after achieving remission. However, frontline treatment with kinase inhibitors (e.g. ibrutinib) is associated with treatment success [24]. In the M13-982 trial, only 5 patients were previously treated with a kinase inhibitor, of whom four achieved a partial remission and one was a non-responder. Further studies are needed to verify a clinical benefit for this critical patient group. However, there is an ongoing trial investigating the efficacy and safety of venetoclax in patients who were previously treated with idelalisib and/or ibrutinib.

limitations inherent to single-arm design and due to the sample size

Due to the single-arm design of the trial, several limitations occur. Interpreting the treatment effect is especially difficult. Besides the comparative efficacy of the treatment, responses may be influenced by an effect of the natural history of the disease. Another limitation due to the lack of a comparator is that a positive effect of the treatment could be missed [27]. In addition, the single-arm design can also lead to various biases besides the treatment effect, that can affect clinical outcomes [28]. Venetoclax should therefore be compared to other treatment options (e.g. kinase inhibitors). This could have the additional advantage of yielding information as to which drug the patients benefit from the most and thus enable the establishment of treatment recommendations based on direct head-to-head comparison data. Furthermore, another limiting factor of the study was the small sample size. To enhance the chance of detecting a true effect, a higher study population would be necessary [29]. Follow-up may have been insufficient to fully determine intended effects, including DOR, PFS, OS, and all potential serious AEs.

potential of developing resistance

Due to considerable selection pressure for cancer cells to escape elimination, the development or selection of resistant clones may be a problem with venetoclax treatment [30]. The mechanism of resistance with venetoclax has not yet been described in CLL patients [31]. One mechanism would be the up-regulation of alternate anti-apoptotic BCL2 family members (e.g. BCL-XL, BCL-W, MCL1 and BCL2A1), like ABT-737 (inhibitor of BCL2 and BCL-XL), which induces resistance by up-regulating BCL-XL and BCL2A1 [32, 33]. Combination therapies with kinase inhibitors or anti-CD20 antibodies may be an option to achieve long-term and complete CLL remission with venetoclax [30, 31]. Two combination therapies are currently under investigation in two phase III trials for the treatment of CLL (NCT02005471 and NCT02242942) [34, 35].

feasible treatment option for patients with relapsed/refractory CLL wit del(17p) deletion

BUT no RCT available, immature data, long-term effects missing, no cost information available

Overall, as no agreed upon standard care exists as yet for the treatment of relapsed or refractory CLL patients with del(17p), venetoclax might be a treatment option for this indication. Nevertheless, although an OR was achieved in 79.4% of patients, only 8% of them showed a CR. Furthermore, a randomised controlled trial (RCT) will be necessary to compare safety and efficacy outcomes in order to reliably interpret the actual treatment effect. Furthermore, mature data is needed to evaluate the efficacy and safety of venetoclax, including in regard to long-term effects and potential resistance mechanisms. There are currently no price estimates available for venetoclax for Austria, but costs incurring as a result of tumour lysis syndrome prophylaxis must be taken into account as well in this regard, if venetoclax receives marketing authorisation in Europe.

# 11 References

[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals.Version 3.0. 2013 2013 [cited 2016-08-10]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Seymour J. ABT-199 for chronic lymphocytic leukemia. Clinical Advances in Hematology and Oncology. 2014;12(10):698-700.

[3] U.S. Food and Drug Administration. Drugs@FDA. Venclexta™. Label information. . 2016 [cited 2016-08-10]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.

[4] Deeks ED. Venetoclax: First Global Approval. Drugs. 2016;76(9):979-87.

[5] Bojarczuk K, Sasi BK, Gobessi S, Innocenti I, Pozzato G, Laurenti L, et al. BCR signaling inhibitors differ in their ability to overcome Mcl-1-mediated resistance of CLL B cells to ABT-199. Blood. 2016;127(25):3192-201.

[6] European Medicine Agency. Public summary of opinion on orphan designation-Venetoclax for the treatment of acute myeloid leukaemia. 2016 [cited 2016-08-10]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2016/04/WC500204479.pdf.

[7] Kanti R Rai M, Stephan Stilgenbauer M. Up to Date - Staging and prognosis of chronic lymphocytic leukemia. 2016 [cited 2016-08-11]; Available from: https://www.uptodate.com/contents/staging-and-prognosis-of-chronic-lymphocytic-leukemia?source=search_result&search=CLL&selectedTitle=1~150.

[8] National Cancer Instiute (NIH). NCI Dictionary of Cancer Terms. CLL. [cited 2016-08-11]; Available from: http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=346545.

[9] Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Am J Hematol. 2015;90(5):446-60.

[10] Sun C, Wiestner A. Prognosis and therapy of chronic lymphocytic leukemia and small lymphocytic lymphoma. 2015. p. 147-75.

[11] Kanti R Rai M, Stephan Stilgenbauer M. Up to Date - Clinical presentation, pathologic features, diagnosis, and differential diagnosis of chronic lymphocytic leukemia. 2016 [cited 2016-08-11]; Available from: https://www.uptodate.com/contents/clinical-presentation-pathologic-features-diagnosis-and-differential-diagnosis-of-chronic-lymphocytic-leukemia?source=see_link.

[12] STATISTIK AUSTRIA. Non-Hodgkin. Krebsinzidenz. Krebsmortalität. [cited 2016-08-11]; Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/non-hodgkin/index.html.

[13] National Cancer Instiute (NIH). SEER Stat Fact Sheets: Chronic Lymphocytic Leukemia (CLL). [cited 2016-08-11]; Available from: http://seer.cancer.gov/statfacts/html/clyl.html.

[14] Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M, Group ObotEGW. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2011;22(suppl 6):vi50-vi4.

[15] Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.

[16] National Cancer Instiute (NIH). Chronic Lymphocytic Leukemia Treatment (PDQ®)–Patient Version. [cited 2016-08-12]; Available from: http://www.cancer.gov/types/leukemia/patient/cll-treatment-pdq.

[17] National Guideline Clearinghouse. Guideline summary.Chronic lymphocytic leukemia. [cited 2016-08-16]; Available from: https://www.guideline.gov/summaries/summary/47859/chronic-lymphocytic-leukemia.

[18] Kanti R Rai M, Stephan Stilgenbauer M. Up to Date - Overview of the treatment of chronic lymphocytic leukemia. [cited 2016-08-16]; Available from: https://www.uptodate.com/contents/overview-of-the-treatment-of-chronic-lymphocytic-leukemia?source=search_result&search=CLL&selectedTitle=2~150.

[19] Kanti R Rai M, Stephan Stilgenbauer M. Up to Date - Treatment of relapsed or refractory chronic lymphocytic leukemia. 2016 [cited 2016-08-16]; Available from: https://www.uptodate.com/contents/treatment-of-relapsed-or-refractory-chronic-lymphocytic-leukemia?source=see_link#H1178511.

[20] Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2016;17(6):768-78.

[21] Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study - Supplementary appendix. The Lancet Oncology. 2016;17(6):768-78.

[22] Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. The New England journal of medicine. 2016;374(4):311-22. Epub 2015/12/08.

[23] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health. 1998;52(6):377-84.

[24] Kanti R Rai M, Stephan Stilgenbauer M. Up to Date - Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia. [cited 2016-08-22]; Available from: http://www.uptodate.com/contents/selection-of-initial-therapy-for-symptomatic-or-advanced-chronic-lymphocytic-leukemia?source=see_link#H5624038.

[25] Moreno C, Montserrat E. Genetic lesions in chronic lymphocytic leukemia: what's ready for prime time use? Haematologica. 2010;95(1):12-5.

[26] Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJS, Bezares RF, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. The Lancet.370(9583):230-9.

[27] Evans SR. Clinical trial structures. Journal of experimental stroke & translational medicine. 2010;3(1):8-18.

[28] Hamre HJ, Glockmann A, Kienle GS, Kiene H. Combined bias suppression in single-arm therapy studies. Journal of Evaluation in Clinical Practice. 2008;14(5):923-9.

[29] Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365-76.

[30] Thijssen R, Slinger E, Weller K, Geest CR, Beaumont T, van Oers MHJ, et al. Resistance to ABT-199 induced by microenvironmental signals in chronic lymphocytic leukemia can be counteracted by CD20 antibodies or kinase inhibitors. Haematologica. 2015;100(8):e302-6.

[31] Woyach JA, Johnson AJ. Targeted therapies in CLL: Mechanisms of resistance and strategies for management. Blood. 2015;126(4):471-7.

[32] Youle RJ, Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. Nat Rev Mol Cell Biol. 2008;9(1):47-59.

[33] Vogler M, Butterworth M, Majid A, Walewska RJ, Sun X-M, Dyer MJS, et al. Concurrent up-regulation of BCL-XL and BCL2A1 induces approximately 1000-fold resistance to ABT-737 in chronic lymphocytic leukemia. Blood. 2009;113(18):4403.

[34] U.S. National Institutes of Health. Study protocol - A Study to Compare the Efficacy and Safety of Obinutuzumab + GDC-0199 Versus Obinutuzumab + Chlorambucil in Patients With Chronic Lymphocytic Leukemia. [cited 2016-08-23]; Available from: https://clinicaltrials.gov/ct2/show/NCT02242942.

[35] U.S. National Institutes of Health. Study protocol - A Study of GDC-0199 (ABT-199) Plus MabThera/Rituxan (Rituximab) Compared With Bendamustine Plus MabThera/Rituxan (Rituximab) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia. [cited 2016-08-23]; Available from: https://clinicaltrials.gov/ct2/show/NCT02005471.

# 12 Appendix

*Table 3: Characteristics of trial M13-982*

| | | | |
|---|---|---|---|
| **Title:** Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study [20, 21] | | | |
| **Study identifier** | *NCT01889186, EudraCT number 2012-004027-20, M13-982* | | |
| **Design** | Phase II, single-arm, open-label, multicentre | | |
| | Duration | | *Enrolment:* May 2013 to June 2014<br>*Median follow-up:* 12.1 months (range: 10.1–14.2)<br>*Data cut-off:* 2015-04-30 |
| **Hypothesis** | Exploratory<br>The study was designed to assess the activity of venetoclax in patients with relapsed/refractory CLL with del(17p). The analysis for the primary study endpoint was pre-specified to be done once 70 patients completed a week 36 assessment (90% power at a two sided α of 5%). | | |
| **Funding** | AbbVie Inc. & Genentech USA, Inc. | | |
| **Treatment group** | Intervention (n = 107) | | Venetoclax with a weekly dose ramp-up schedule (20, 50, 100, 200, 400 mg) over 4–5 weeks until a continuous daily dose of 400 mg had been reached – oral |
| **Endpoints and definitions** | Activity of venetoclax monotherapy (primary endpoint) | - | Measured by the proportion of patients who achieved an overall response (OR; partial remission or higher) assessed by an independent review committee |
| | Time to first response | TTR | Time from first dose to first response |
| | Progression-free survival | PFS | Number of days from the date of first dose to the date of earliest disease progression or death |
| | Overall survival | OS | Number of days from the date of first dose to the date of death for all dosed patients |
| | Duration of overall response | DOR | Number of days from the date of first response to the earliest recurrence or disease progression per the independent review committee assessment |
| **Results and analysis** | | | |
| **Analysis description** | **Primary analysis**<br>The primary endpoint was assessed once 70 patients completed a week 36 assessment.<br>Safety and all other activity analyses were assessed in the per-protocol population. | | |

<table>
<tr><td colspan="3">Title: Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study [20, 21]</td></tr>
<tr><td>Study identifier</td><td colspan="2">NCT01889186,EudraCT number 2012-004027-20, M13-982</td></tr>
<tr><td rowspan="3">Analysis population</td><td>Inclusion</td><td>✲ Age ≥ 18 years<br>✲ Diagnosed CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines<br>✲ Indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines<br>✲ Measurable disease (lymphocytosis > 5 × 10⁹/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)<br>✲ Refractory/relapsed disease after receiving at least one prior line of therapy or previously untreated CLL<br>✲ del(17p) > 7% of cells in peripheral blood (assessed by local or central laboratory)<br>✲ ECOG performance status of 0–2<br>✲ Adequate bone marrow function:<br>- ANC ≥ 1000/µL<br>- ANC < 1000/µL at screening, and bone marrow heavily infiltrated with underlying disease; growth factor support may be administered after screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria<br>- Platelets > 30,000/mm³<br>- Haemoglobin ≥ 8.0 g/dL<br>✲ Adequate coagulation, renal, and hepatic function, per laboratory reference range at screening:<br>- aPTT and PT not to exceed 1.5 × the upper limit of normal<br>- Calculated creatinine clearance > 50 mL/min<br>- AST and ALT ≥ 3.0; Bilirubin ≥ 1.5<br>✲ For high-risk tumour lysis syndrome patients a pre-approval by the AbbVie medical monitor is required prior to enrolment</td></tr>
<tr><td>Exclusion</td><td>✲ Performed allogeneic stem cell transplant<br>✲ Confirmed Richter's transformation (by biopsy)<br>✲ Prolymphocytic leukaemia<br>✲ Active and uncontrolled autoimmune cytopenia (for two weeks prior to screening), compromising autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura despite low-dose corticosteroids<br>✲ Prior treatment with venetoclax<br>✲ Biologic agent given with anti-neoplastic intent within 30 days prior to the first dose of venetoclax<br>✲ Patient had received one of the following within 14 days or five half-lives, as applicable, prior to the first dose of the study drug, or has not recovered to less than CTC grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:<br>▪ - Any anti-cancer therapy including chemotherapy or radiotherapy<br>▪ - Investigational therapy, including targeted small-molecule agents<br>✲ Allergy to both xanthine oxidase inhibitors and rasburicase</td></tr>
<tr><td colspan="2"><table>
<tr><td>Characteristics</td><td>Venetoclax</td></tr>
<tr><td>Median age (range), years<br>≥ 65 years, n (%)<br>< 65 years, n (%)</td><td>67 (37–85)<br>61 (57)<br>46 (43)</td></tr>
<tr><td>Gender, n (%)</td><td>♀ 37 (35)<br>♂ 70 (65)</td></tr>
<tr><td>ECOG performance status, n (%)<br>0<br>1<br>2</td><td><br>42 (39)<br>56 (52)<br>9 (8)</td></tr>
</table></td></tr>
</table>

| **Title:** Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study [20, 21] | | |
|---|---|---|
| **Study identifier** | *NCT01889186,EudraCT number 2012-004027-20, M13-982* | |
| **Analysis population** *(continuation)* | Rai stage at study entry | |
| | Stage III | 19 (18) |
| | Stage IV | 32 (30) |
| | Other | 56 (52) |
| | Binet stage at study entry | |
| | Stage A–B | 65 (61) |
| | Stage C | 42 (39) |
| | Previous treatments, n (%)[4] | |
| | Median number of previous treatments (range) | 2 (1–4) |
| | Bendamustine | 54 (50) |
| | Bendamustine refractory | 38 (70) |
| | Fludarabine | 78 (73) |
| | Fludarabine refractory | 34 (44) |
| | Bendamustine or fludarabine refractory | 62 (58) |
| | Idelalisib | 1 (1) |
| | Ibrutinib | 3 (3) |
| | Other B-cell receptor inhibitors | 1 (1) |
| | Bulky disease | |
| | One or more nodes ≥ 5 cm | 57 (53) |
| | No nodes ≥ 5 cm | 50 (47) |
| | *TP53* mutation[5] | |
| | Yes | 60 (56) |
| | No | 17 (16) |
| | Intermediate | 6 (6) |
| | Missing | 24 (22) |
| | *IGHV* mutation | |
| | Yes | 7 (7) |
| | No | 30 (28) |
| | Missing | 70 (65) |
| | 11q deletion | |
| | Deleted | 30 (28) |
| | Not deleted | 77 (72) |
| | Absolute lymphocyte count | |
| | ≥ 25 x $10^9$ cell per L | 54 (50) |
| | < 25 x $10^9$ cell per L | 53 (50) |
| | Median (x$10^9$) | 25.8 (7.9–8.9) |
| | Serum β-2 microglobulin | |
| | < 3 mg/L | 4 (4) |
| | ≥ 3 mg/L | 13 (12) |
| | Missing | 90 (84) |
| | Disease-related complications | |
| | Neutropenia | 24 (22) |
| | Anaemia | 22 (21) |
| | Thrombocytopenia | 16 (15) |
| | Tumour lysis syndrome risk category | |
| | Low | 19 (18) |
| | Medium | 43 (40) |
| | High | 45 (42) |

[4] Refractory status was defined as no response or disease progression within 6 months of treatment

[5] Investigator reported

| **Title:** Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label phase 2 study [20, 21] | |
|---|---|
| **Study identifier** | *NCT01889186,EudraCT number 2012-004027-20, M13-982* |
| **Critical appraisal** | |
| **Study strengths** | ✪ The study objective, patient characteristics, main outcomes, findings, and estimates of variability were clearly described.<br>✪ Withdrawals and losses to follow-up were fully reported.<br>✪ Appropriate statistical tests were used to evaluate results and the probability value was reported for the main outcome.<br>✪ An independent review committee assessed ORR defined as partial remission or higher. |
| **Study limitations** | ✪ Insufficient follow-up to determine intended effects (DOR based on 13 events), (PFS – 31 events), (OS – 17 deaths) and all potential serious AEs.<br>✪ Per-protocol analysis, where a comparison of treatment includes only those patients who completed the treatment originally allocated, may lead to bias. Intention-to-treat analysis, a comparison of treatment groups that includes all patients as originally allocated, may be used to reduce the potential for bias.<br>✪ Risk of overestimate of effect in using an open-label, single-arm, cohort study design with historical control to determine overall ORR as patients may have been recruited, selected, or assessed differently over time. A simultaneous control group would control for > 1 confounder; an RCT with adequate generation of randomisation, concealment of allocation and blinded assessment would reduce the risk of overestimating the effect.<br>✪ Study subjects may not be generalisable to the population or representative of the population from whom they were derived. Patient selection sampling was not fully reported, nor was the proportion of the population sampled.<br>✪ The funders participated in the study design, conduct, analysis, interpretation of data, writing, review and publication. |

*Abbreviations: ALT = alanine aminotransferase, ANC = absolute neutrophil count, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, CLL = chronic lymphocytic leukaemia, CTC = Common Toxicity Criteria, DOR = duration of response, IWCLL NCI-WG = International Workshop for Chronic Lymphocytic Leukaemia –National Cancer Institute-Working Group, ECOG = Eastern Cooperative Oncology Group, OS = overall survival, PFS: progression free survival, PT = prothrombin time*

*Table 4: Study quality assessment by Downs and Black [23]*

| Assessment of study quality, modified Downs and Black checklist for randomised and non-randomised studies | | |
|---|---|---|
| **Reporting** | Yes/No/Partially | Score |
| 1. Is the objective of the study clear? | Yes=1, No=0 | |
| 2. Are the main outcomes clearly described in the Introduction or Methods? | Yes=1, No=0 | |
| 3. Are characteristics of the patients included in the study clearly described? | Yes=1, No=0 | |
| 4. Are the interventions clearly described? | Yes=1, No=0 | |
| 5. Are the distributions of principal confounders in each group of subjects clearly described? | Yes=2, Partially=1, No=0 | |
| 6. Are the main findings of the study clearly described? | Yes=1, No=0 | |
| 7. Does the study estimate random variability in data for main outcomes? | Yes=1, No=0 | |
| 8. Have all the important adverse events consequential to the intervention been reported? | Yes=1, No=0 | |
| 9. Have characteristics of patients lost to follow-up been described? | Yes=1, No=0 | |
| 10. Have actual probability values been reported for the main outcomes except probability < 0.001? | Yes=1, No=0 | |
| 11. Is the source of funding clearly stated? | Yes=1, No=0 | |
| **External validity** | Yes/No/Unclear | Score |
| 12. Were subjects asked to participate in the study representative of the entire population recruited? | Yes=1, No=0, Unclear=0 | |
| 13. Were those subjects who were prepared to participate representative of recruited the population? | Yes=1, No=0, Unclear=0 | |
| 14. Were staff, places and facilities where patients were treated representative of the treatment most received? | Yes=1, No=0, Unclear=0 | |
| **Internal validity** | Yes/No/Unclear | Score |
| 15. Was an attempt made to blind study subjects to the intervention? | Yes=1, No=0, Unclear=0 | |
| 16. Was an attempt made to blind those measuring the main outcomes? | Yes=1, No=0, Unclear=0 | |
| 17. If any of the results of the study were based on data dredging, was this made clear? | Yes=1, No=0, Unclear=0 | |
| 18. Was the time period between intervention and outcome the same for the intervention and control groups or adjusted for? | Yes=1, No=0, Unclear=0 | |
| 19. Were statistical tests used to assess main outcomes appropriate? | Yes=1, No=0, Unclear=0 | |
| 20. Was compliance with the interventions reliable? | Yes=1, No=0, Unclear=0 | |
| 21. Were main outcome measures used accurate? (valid and reliable) | Yes=1, No=0, Unclear=0 | |
| **Internal validity-cofounding (selection bias)** | Yes/No/Unclear | Score |
| 22. Were patients in different intervention groups recruited from the same population? | Yes=1, No=0, Unclear=0 | |
| 23. Were study subjects in different intervention groups recruited over the same period of time? | Yes=1, No=0, Unclear=0 | |
| 24. Were study subjects randomised to intervention groups? | Yes=1, No=0, Unclear=0 | |
| 25. Was the randomised intervention assignment concealed from patients and staff until recruitment was complete? | Yes=1, No=0, Unclear=0 | |
| 26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn? | Yes=1, No=0, Unclear=0 | |
| 27. Were losses of patients to follow-up taken into account? | Yes=1, No=0, Unclear=0 | |
| **Power** | Size of smallest intervention group Score 0-5 | Score |
| 28. Was the study sufficiently powered to detect clinically important effects where the probability value for a difference due to chance is < 5%? | | |