Horizon Scanning in Oncology

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Health Technology Assessment

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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 A working version (unpublished) of V3.0 of the Model was used.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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Abstract

Introduction

Constitutive Bruton tyrosine kinase (BTK) activation is associated with B-cell proliferation and lymphoma progression. In patients with Waldenström's macroglobulinemia (WM), a highly prevalent somatic mutation in the Myeloid Differentiation 88 signalling adaptor (MYD88 L265P) potentiates cell survival through BTK activation of nuclear factor kappa B (NFκB). Ibrutinib, a first-generation BTK inhibitor, selectively and irreversibly binds BTK, blocking B-cell receptor signaling and inducing apoptosis in WM cells harboring the MYD88 mutation.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials.

Results of the iNNOVATE trial

In the phase III, iNNOVATE trial, 150 symptomatic treatment naïve or relapsed/refractory WM patients were randomised 1:1 to 420 mg oral ibrutinib or placebo daily, in combination with 375 mg/m^2 rituximab IV once weekly for four weeks, followed by another four-week course after a three-month interval. Adding ibrutinib prolonged progression-free survival (PFS) by 54%, conferring a longer PFS than rituximab alone (not reached versus 20.3 months, respectively) and reducing the relative risk of progression or death by 80%. The PFS benefit was observed regardless of previous treatment, MYD88 or C-X-C chemokine receptor type 4 (CXCR4) genotype, or prognostic score. At 30 months, the overall survival (OS) rates were 94% versus 92% for ibrutinib- and placebo combination, respectively, with permitted crossover for patients in the placebo arm to ibrutinib single in the case of progression; median OS was not reached in either group. Adding ibrutinib increased the overall response rate (ORR) by 45% compared with rituximab alone, largely independent of the genotype. Adding ibrutinib to rituximab therapy increased the number of patients with sustained haemoglobin (Hb) by 32% and resulted in fewer immunoglobulin M (IgM) flares (8% versus 47%, respectively). Atrial fibrillation and bleeding events were 12% and 30% more common in patients receiving ibrutinib combination versus rituximab alone, respectively.

Conclusion

Overall, adding ibrutinib to rituximab therapy increases PFS and ORR, and reduces the risk of death and progression for symptomatic WM patients with untreated or recurrent disease. Consistent PFS and OR benefit were observed regardless of line, genotype or prognostic score. Further evaluation is needed to identify the role of ibrutinib as first-line versus salvage therapy; monotherapy versus in combination with biologic agents, other small molecules or chemoimmunotherapy; optimal duration of treatment; management of ibrutinib intolerant or resistant patients; and the comparative safety and effectiveness with new BTK inhibitors.

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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 pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is ibrutinib?
A0022	Who manufactures ibrutinib?
A0007	What is the target population in this assessment?
A0020	For which indications has ibrutinib received marketing authorisation?
Health problem and current use	
A0002	What is Waldenström's macroglobulinemia?
A0004	What is the natural course of Waldenström's macroglobulinemia?
A0006	What are the consequences of Waldenström's macroglobulinemia for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of disease or health condition?
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D0001	What is the expected beneficial effect of ibrutinib on mortality?
D0005	How does ibrutinib affect symptoms and findings (severity, frequency) of Waldenström's macroglobulinemia?
D0006	How does ibrutinib affect progression (or recurrence) of Waldenström's macroglobulinemia?
D0011	What is the effect of ibrutinib on patients' body functions?
D0012	What is the effect of ibrutinib on generic health-related quality of life?
D0013	What is the effect of ibrutinib on disease-specific quality of life?
Safety	
C0008	How safe is ibrutinib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying ibrutinib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ibrutinib?
A0021	What is the reimbursement status of ibrutinib?

2 Drug description

Generic/Brand name/ATC code:

Ibrutinib/Imbruvica®/L01xE27/PCI-32765

B0001: What is ibrutinib?

first-generation BTK inhibitor

Constitutive Bruton tyrosine kinase (BTK) activation is associated with B-cell proliferation and the progression of B-cell lymphomas. In patients with Waldenström's macroglobulinemia (WM), a highly prevalent somatic mutation in WM MYD88 L265P potentiates cell survival through BTK activation of nuclear factor kappa B (NFκB) [2]. Ibrutinib, a first-generation BTK inhibitor, selectively and irreversibly binds BTK, blocking B-cell receptor signalling and inducing apoptosis in WM cells harbouring the MYD88 mutation [3].

420 mg oral ibrutinib once/day + two 4-week courses of rituximab (375 mg/m² IV)

Ibrutinib is available in 90- and 120-capsule bottles of 140 mg capsules. It is administered as three 140 mg oral capsules, taken with eight ounces of water once daily, until disease progression or unacceptable toxicity [4]. Patients also receive 375 mg/m^2 rituximab by intravenous (IV) infusion once weekly for four weeks, followed by another four-week rituximab course after a three-month interval [5].

monitor CBC, ECG, renal and hepatic function; reduce/interrupt dose/discontinue for safety/tolerability

Prior to initiating ibrutinib, patients undergo baseline renal and hepatic function tests, and coagulation status. Those with cardiac risk factors, a history of atrial fibrillation, or acute infections require a baseline electrocardiogram (ECG) prior to starting ibrutinib. Patients receiving ibrutinib undergo monthly complete blood counts (CBC) and monitoring for symptoms of atrial fibrillation, infection, hepatitis B reactivation, fever, tumour lysis syndrome, and hypertension. Serum creatinine levels are monitored periodically in patients with renal impairment. Due to the risk for increased bleeding, ibrutinib is not for use in patients with moderate or severe hepatic impairment; a dose reduction to 140 mg may be considered in patients with mild hepatic impairment. Patients should avoid concomitant use of strong CYP3A inhibitors or inducers, grapefruit or Seville oranges, anticoagulants or platelet inhibitors, or medications that prolong the QT interval [4].

A0022: Who manufactures ibrutinib?

Janssen Inc and Pharmacyclics LLC (an AbbVie company)

3 Indication

A0007: What is the target population in this assessment?

Ibrutinib (Imbruvica®) is indicated, in combination with rituximab, for previously untreated Waldenström's macroglobulinemia (WM) and for those with rituximab-sensitive disease recurrence.

previously untreated and rituximab-sensitive recurrent WM

4 Current regulatory status

A0020: For which indications has ibrutinib received marketing authorisation?

In January 2015, the US Food and Drug Administration (FDA) approved ibrutinib monotherapy for the treatment of relapsed or refractory WM through the Breakthrough Therapy Designation Pathway. Approval was based on the overall response rate (ORR) reported in a phase II multicentre study [6]. In August 2018, the approval was expanded to include combination use with rituximab across all lines of therapy for WM. This chemotherapy-free combination for WM was approved based on 30-month progression-free survival (PFS) rates reported in the herein-assessed phase III iNNOVATE trial [7, 8].

FDA approvals:

monotherapy for pre-treated WM in 2015; in combination with rituximab for WM in August 2018

Ibrutinib was granted its first approval by the FDA in November 2013 for the treatment of relapsed or refractory mantle cell lymphoma (MCL). The accelerated approval was based on ORR and PFS data reported in a phase II study [9, 10]. From 2014 to 2016, the FDA expanded approval for use in previously-treated chronic lymphocytic leukaemia (CLL) for patients with or without a genetic mutation in chromosome 17 (del 17p), and as first-line therapy. The indication was further expanded, in May 2016, to include patients with small lymphocytic lymphoma (SLL). In 2017, ibrutinib underwent accelerated approval for relapsed or refractory marginal zone lymphoma (MZL) in patients requiring systemic therapy after anti-CD20-based therapy, and expanded approval for previously-treated chronic graft versus host disease (cGVHD) [4].

relapsed/refractory MCL, any-line CCL, SLL, pre-treated MZL requiring systemic therapy after anti-CD20-based therapy; pre-treated cGVHD

Ibrutinib received orphan medicine status by the European Medical Agency (EMA) in 2012 for the treatment of CLL, and is approved as second-line therapy for MCL, any-line monotherapy for CLL, and in combination with bendamustine and rituximab for previously-treated CLL. Ibrutinib was granted orphan designation for the treatment of MZL in August 2015 and GVHD in 2016 [11, 12]. In July 2015, ibrutinib received European Commission (EC) approval as monotherapy for relapsed and refractory WM, or as first-line therapy for patients unsuitable for immunochemotherapy [13, 14]. There is currently no indication as to when the EMA may receive a marketing authorisation application (MAA) to extend the use of ibrutinib in combination with rituximab for WM based on results of the iNNOVATE trial.

EMA approvals:

2nd-line MCL, any-line for CCL, in combination with bendamustine and rituximab for pre-treated CLL, MZL, GVH; monotherapy for pre-treated WM or 1st- line for those unsuitable for immunochemotherapy

5 Burden of disease

A0002: What is Waldenström's macroglobulinemia?

WM: B-cell non-Hodgkin lymphoma; BM infiltration, increased IgM

WM or lymphoplasmacytic lymphoma, is an indolent B-cell non-Hodgkin lymphoma (NHL) affecting lymphoplasmacytoid and plasma B-cells. It is characterised by an accumulation of malignant B-cells in the bone marrow (BM) and an overproduction of abnormal monoclonal protein immunoglobulin (Ig) M or macroglobulin in the blood [15]. Approximately 91% of WM patients have a leucine to proline somatic mutation (MYD88 L265P) in the Myeloid Differentiation 88 signalling adaptor (MYD88) [6]. Somatic mutations reminiscent of Warts, Hypogammaglobulinemia, Infections, and Myelokathesis (WHIM) in the C-X-C chemokine receptor type four have been observed in 27–40% of WM patients. These mutations may be nonsense (CXCR4 WHIM/NS) or frameshift (CXC44 WHIM/FS) mutations resulting in the formation of a truncated receptor protein. In tumour cells, MYD88 L265P constitutively activates NF-κB through two distinct pathways involving BTK and the interleukin-1 receptor-associated kinases (IRAK1 and IRAK4) to potentiate cell survival [16].

MYD88 L265P and WHIM-like CXCR4 mutations in 91% and 27-40% of WM patients, resp.

MYD88 L265P and CXCR4 WHIM/NS or FS: severe disease

MYD88 L265P: better outcomes

The MYD88 L265P with CXCR4 WHIM/FS genotype is associated with severe disease, greater BM involvement, and increased likelihood of developing viscosity-related complications with higher serum IgM levels compared to those of MYD88 L265P/CXCR4 WHIM/NS genotype. Patients with MYD88 Wild Type (WT)/CXCR4 WT have the lowest BM involvement. Despite the association of severe disease with MYD88 L265P/CXCR4 WHIM/NS or FS mutations compared to MYD88 WT/CXCR4 WT, survival outcomes do not appear to be affected by the presence of CXCR4 mutations. Better outcomes are observed in patients with MYD88 L265P genotype compared to those with MYD88 WT genotype, and the risk of death is tenfold less. The presence of MYD88 and CXCR4 mutations affects responsiveness to ibrutinib. [17, 18].

A0004: What is the natural course of Waldenström's macroglobulinemia?

malignant B-cells infiltrate BM, disrupt haematopoiesis; metastasize to lymph nodes, liver, spleen, stomach, intestines, lungs

Approximately 25% of WM patients are asymptomatic at diagnosis and are considered to have smouldering WM (SWM). Patients with IgM protein <3 g/dL are considered to have IgM monoclonal gammopathy of undetermined significance (IgM-MGUS). As malignant B-cells grow mainly in the BM, they disrupt normal haematopoiesis of erythrocytes, white cells and platelets. Low levels of red blood cells result in anaemia and fatigue, low white blood cells increase the risk of infection, and low platelets cause increased bleeding and bruising. While active WM typically involves the BM, it progresses over time causing abnormal blood cells, known as B lymphocytes, to grow within the lymph nodes, liver, spleen, stomach, intestines or lungs. While rare, WM may progress to multiple myeloma [15, 16].

A0006: What are the consequences of Waldenström's macroglobulinemia for the society?

The overall survival (OS) rate of smoldering WM approximates that of the average age-matched population [19]. During a 15-year follow-up study, the rate of progression of smoldering WM to symptomatic WM was 71% and the cumulative risk of progression of smoldering WM to symptomatic WM, amyloidosis, or a related disorder was 6% at one year, 39% at three years, 59% at five years, and 68% at ten years [20]. The overall relative five-year survival of those with WM is approximately 78%. Median survival rates for patients of low-, intermediate-, and high-risk according to the International Prognostic Scoring System for WM (IPSSWM) are 12, 8, and 3.5 years, respectively [21, 22].

IPSSWM risk-stratified median OS:

low: 12 years
intermediate: 8 years
high: 3.5 years

A0023: How many people belong to the target population?

WM represents approximately 1–3% of all NHLs. Of the 1,318 new cases of NHLs diagnosed in 2015, approximately 26 are due to WM [23]. According to the European WM network, five in 1,000,000 people per year are diagnosed with WM [24]. The incidence rate is higher in men than women, 3.4 versus 1.7 per million, respectively, with a median age of diagnosis of between 63 and 68 years [15, 25]. Incidence is higher among Americans of European descent, while African American descendants represent approximately 5% of all patients [18].

WM:
5 in 1,000,000 people/year

incidence: higher in older Caucasian males of European descent

A0005: What are the symptoms and the burden of disease or health condition?

Patients with WM exhibit symptoms related to increased serum IgM and/or BM lymphoplasmacytic infiltration. B symptoms include recurrent fever, night sweats, and weight loss. Fatigue is associated with anaemia (haemoglobin [Hb] ≤10 g/dL), bleeding results from thrombocytopenia (<100 g/L), and infections may occur due to low white blood cells. An overproduction of serum macroglobulin can cause peripheral neuropathy, impaired kidney function, and systemic amyloidosis with organ damage. A large accumulation of IgM proteins (>50 g/L) in the blood causes hyperviscosity syndrome in 10–30% of WM patients. Associated symptoms include bleeding from the nose, gums or lining of the gastrointestinal tract, headache, vertigo, blurred vision, altered mental status and shortness of breath. Symptomatic hyperviscosity syndrome requires plasmapharesis. Approximately 10% of WM patients have acquired haemolytic anaemia where red blood cells are destroyed by macroglobulin when a patient encounters a low temperature environment. Up to 20% of WM patients develop cryoglobulinemia where macroglobulin in the blood becomes thick when exposed to cold temperatures causing circulatory problems [15].

WM symptoms:

fever, night sweats, weight loss, fatigue, bleeding, infection, neuropathy, impaired kidney function, systemic amyloidosis

A0003: What are the known risk factors for Waldenström's macroglobulinemia?

IPSSWM: risk based on 5 adverse covariates —age, Hb, platelet count, ß2-microglobulin, and serum IgM

WM is staged based on the patient's risk status using the IPSSWM. Overall, five adverse covariates have been identified, including age >65 years, Hb ≥11.5 g/dL, platelet count ≤100,000/mm^3, ß2-microglobulin level >3 mg/L, and serum IgM level >7.0 g/dL. Patients at low risk are less than 65 years of age with fewer than two adverse covariates. Patients at intermediate risk are over 65 years of age and have two adverse covariates [15]. High-risk patients have two or more adverse covariates. First-degree relatives of WM patients have a 20-fold increased risk of developing WM, and a three- to five-fold increased risk of developing another NHL, CLL, or IgM-MGUS [26]. People with chronic hepatitis C infection or autoimmune diseases may also be at increased risk for WM [21].

A0024: How is Waldenström's macroglobulinemia currently diagnosed according to published guidelines and in practice?

diagnosis:

BM biopsy and immunophenotyping

genotyping for MYD88 L265P and CXCR4 mutations

According to The Second International Workshop on WM (IWWM), active WM is diagnosed based on the detection of BM lymphoplasmacytic infiltration and serum IgM monoclonal protein identified through BM biopsy and immunophenotyping [27]. The typical immunophenotypic profile of the infiltrate is surface IgM+, CD5±, CD10-, CD19+, CD20+, CD22+, CD23-, CD25+, CD27+, FMC7+, CD103-, and CD138+ [16]. Whole genome or paired tumour/normal sequencing is used to detect the highly recurrent MYD88 L265P mutation and frameshift or nonsense CXCR4 mutations present in approximately 91% and 27–40% of WM patients, respectively. Tumour burden and treatment response are evaluated by performing serum immunoelectrophoresis, immunoglobulin measurement, CT scans involving pelvis, abdomen, chest and cervical area, cold agglutin, and cryoglobulins measurements [27, 28].

6 Current treatment

A0025: How is Waldenström's macroglobulinemia currently managed according to published guidelines and in practice?

surveillance: IgM-GUS and SWM

treatment per IPSSWM risk-stratification

Approximately 25% of WM patients are asymptomatic at diagnosis; those with IgM-GUS or SWM with preserved marrow function undergo surveillance. According to the Second IWWM, therapy is indicated when patients report WM-related constitutional symptoms [15]. Currently, there is no single or combination standard treatment used for all patients. WM patients may be treated with alkylating and other chemotherapy agents, purine nucleoside analogues, monoclonal antibodies, corticosteroids, immunomodulatory agents and proteasome inhibitors used as monotherapy or in combination. Treatment per IPSSWM risk-stratification involves the following options [15, 27, 28]:

1st-line:

rituximab monotherapy, DRC, bortezomib- or carfilzomib-based regimens, bendamustine-rituximab, ibrutinib, and plasmapheresis

- Newly diagnosed patients with hyperviscosity require therapeutic plasma exchange prior to cytoreductive therapy.
- Rituximab is indicated for untreated WM with symptomatic mild to moderate anaemia, symptomatic cryoglobulinemia (in combination with steroids), or haemolytic anaemia unresponsive to corticosteroids.
- First-line therapy for WM involves 4–6 cycles of bendamustine and rituximab.
- Carfilzomib-based regimens offer a neuropathy-sparing option for untreated WM patients.
- Dexamethasone-rituximab-cyclophosphamide (DRC) or oral fludarabine for treatment-naïve elderly patients when the disease burden is low.
- A bortezomib-based combination (bortezomib-rituximab-dexamethasone) for patients with high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia, amyloidosis, and renal impairment provided the patients' underlying peripheral neuropathy is of grade ≤2.
- Ibrutinib monotherapy for treatment-naïve patients that are not suitable for chemoimmunotherapy, those with a MYD88 mutation irrespective of the presence of CXC4 mutation, and for relapsing WM.
- Previously-treated WM patients that are intolerant to rituximab may benefit from ofatumumab.
- Everolimus or purine analogues are suitable in selected patients with refractory or multiply relapsed disease.
- Relapsing patients may repeat a previous therapy if they achieved durable remission without toxicity to prior therapy.
- Autologous stem cell transplantation (ASCT) should be considered for first or second relapse in transplant-eligible patients with chemosensitive disease.

2nd-line:

ofatumumab, nucleoside analogues, ibrutinib, everolimus, immunomodulatory agents, and ASCT

7 Evidence

systematic literature search in 5 databases: 103 hits

manual search: 20 additional references

overall: 123 references included: 2 studies

A literature search was conducted on 11 October 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "ibrutinib", "imbruvica", "Waldenstroms Macroglobulinemia", "Waldenstrom Macroglobulinemia", "lymphoplasmacytic lymphoma" and "rituximab". The manufacturer was also contacted and submitted a reference that had already been identified by systematic literature search [7], along with an accompanying oral presentation [29]. A manual search identified five statistical reports [17, 20, 21, 25, 26], two FDA approval documents [4, 8], three EMA marketing authorization documents [11, 12, 14], four clinical guidance documents [6, 15, 19, 24], four clinical trial articles [5, 9, 10, 30], and two cost documents [23, 31].

Overall, 122 references were identified. Included in this reported are:

- iNNOVATE, phase III [5, 7, 29, 30]

- Ibrutinib in previously treated WM, phase II study [6]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [32]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

external validity

The external validity of the included trial was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting [33].

ESMO-MCBS could not be assessed

The evaluation of the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was not applied, since it can only be used for the evaluation of solid tumour drugs [34].

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

iNNOVATE: ibrutinib + rituximab versus placebo + rituximab for symptomatic untreated WM or disease recurrence

iNNOVATE (NCT02165397) is a multicentre, double-blind, randomised, interventional phase III trial involving 150 patients with symptomatic untreated WM or disease recurrence [7]. The study was designed to evaluate whether adding ibrutinib to rituximab prolongs PFS and ORR in WM patients compared to rituximab alone. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved all patients who received at least one dose of the study drug; all randomly assigned patients received at least one dose of ibrutinib or placebo in combination with rituximab.

ITT (n = 150): stratified by IPSSWM score, number of prior regimens, and ECOG performance status

Eligible patients were 18 years or older, with centrally confirmed symptomatic untreated or previously treated WM, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients were excluded if they had known central nervous system (CNS) involvement, bleeding disorders, active systemic infection or cardiovascular disease, history of stroke or intracranial haemorrhage, prior BTK therapy, hypersensitivity or resistance to rituximab-containing therapy, or received rituximab within twelve months of study entry. Study participants were stratified according to IPSSWM score at screening (low versus intermediate versus high), number of prior regimens (0 versus 1 or 2 versus ≥3), and ECOG performance-status (0 or 1 versus 2; range from 0 to 5).

420 mg ibrutinib + rituximab versus placebo + rituximab

median DOT: 25.8 months for ibrutinib combination versus 15.5 months for placebo combination

Patients were randomised 1:1 to 420 mg of oral ibrutinib or placebo until disease progression or toxicity. Patients also received 375 mg/m^2 rituximab IV once weekly for four weeks, followed by another four-week rituximab course after a three-month interval [5]. Patients on placebo were allowed to cross over to receive ibrutinib after disease progression as confirmed by the blinded independent review committee (BICR). Dose reductions or interruptions were allowed for any potentially study drug-related event and discontinued if toxicities persist or recur following two dose reductions. The median duration of treatment (DOT) was 25.8 months (range 1.0 to 37.2 months) for patients receiving ibrutinib combination and 15.5 months (range 0.4 to 34.3) for those receiving placebo combination.

death/progression at data cut-off: 50 events

40% cross-over to ibrutinib

At data cut-off, 50 events of disease progression or death had occurred. In the ITT population, 75% (56/75) of ibrutinib combination and 35% (26/75) of placebo combination patients were still receiving the assigned treatment. In the placebo combination group, 40% (30/75) crossed over to ibrutinib following BIRC-assessed (blinded independent review committee-assessed) disease progression during the trial and three (4%) patients received ibrutinib outside of the trial. During a median follow-up of 26.5 months, four deaths occurred in the ibrutinib combination group and six occurred in the placebo combination group.

primary endpoint: BICR-assessed PFS

secondary endpoints: ORR, TTNT, Hb improvement, OS, FACIT-fatigue and safety

exploratory endpoints: investigator-assessed PFS and ORR, DOR, CRR, IgM, HgB

The primary endpoint was PFS, as assessed by the BIRC, based on the modified Consensus Response Criteria from the VIth International Workshop for WM, National Cancer Care Network. Secondary endpoints included BICR-assessed ORR; time to next treatment (TTNT); rate of sustained Hb improvement; proportion of patients with ≥3 point increase from baseline by week 25 in the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue subscale score; OS and safety. Exploratory endpoints included investigator-assessed PFS and ORR, duration of response (DOR); clinical response rate (CRR, ≥minor response [MR]); IgM, HgB, lymph nodes and spleen measures, tumour involvement of BM, EQ-5D-5L visual analogue scale and utility score, Functional Assessment of Cancer Therapy–Anaemia (FACT-An) total score and subscale scores. During treatment, endpoints were assessed every four weeks for 16 weeks, and every eight weeks thereafter until disease progression. The mutational status of MYD88 and CXCR4 were assessed from BM samples obtained from patients prior to starting therapy. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria (CTCAE) version 4.03.

ITT: median age 69 years, 80% intermediate/high prognostic score; 85% previously received rituximab

genotypes: MYD88 L265: 85% CXCR4 WHIM: 36%

The ITT population (n = 150) had a median age of 69 years (range 36–89), 66% were male, 79% had extra-medullary disease, 80% had an intermediate or high prognostic score, and 45% were treatment-naïve. Patients with relapsed disease had received a median of two prior therapies (range 1–6); of these, 85% were previously treated with rituximab. Of the 136 patients for whom baseline mutational data were available, MYD88 L265P and CXCR4 WHIM genotypes were found in 85% and 36%, respectively. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 4 and study quality is described in Table 5 of the appendix, respectively. Clinical efficacy data are presented in

Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

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

median OS: not reached in either group

30 month OS rate: ibrutinib + rituximab: 94% placebo + rituximab: 92%

The secondary endpoint of BICR-assessed median OS was not reached in either group. At a median follow-up of 26.5 months, four deaths had occurred in the ibrutinib combination group during long-term follow-up and six had occurred in the placebo combination group during treatment. The 30-month OS rate was 94% for ibrutinib combination versus 92% for placebo combination. Following BICR-assessed disease progression, 30 placebo combination patients crossed over to receive ibrutinib and three patients received ibrutinib outside of the trial.

D0006: How does ibrutinib affect progression (or recurrence) of Waldenström's macroglobulinemia?

30-month PFS rate: ibrutinib + rituximab: 82% placebo + rituximab: 28%

At 30 months, the primary endpoint, rate of PFS was 82% in the ibrutinib combination group and 28% in the placebo combination group (median, not reached versus 20.3 months; hazard ratio [HR] for progression or death 0.20, 95% confidence interval [CI] 0.11–0.38; $p < 0.001$). Investigator-assessed PFS was similar (HR 0.22, 95% CI 0.12–0.40; $p < 0.001$).

consistent PFS benefit across subgroups regardless of line

The PFS benefit of ibrutinib combination over placebo combination was demonstrated across predefined subgroups in both untreated WM and relapsed disease ($n = 68$ treatment naïve, HR 0.34, 95% CI 0.12–0.95; $p < 0.001$; $n = 82$ relapsed disease, HR 0.17, 95% CI 0.08–0.36; $p < 0.001$). At 24 months, the PFS rate among treatment naïve patients was 84% in the ibrutinib combination group and 59% in the placebo combination group. Since untreated WM patients were enrolled following a protocol amendment, 30-month PFS rates could not be estimated. In patients with disease recurrence, the 24-month PFS rate was 80% in the ibrutinib combination group and 37% in the placebo combination group; and 80% and 22%, respectively at 30 months.

PFS benefit across genotype or IPSSWM prognostic score

The PFS benefit of ibrutinib combination over placebo combination was also consistent across different MYD88 and CXCR4 genotypes and IPSSWM prognostic scores. At 30 months, PFS rates were 86% versus 33% among patients with the MYD88 L265P/CXCR4 WT genotype, 80% versus 29% among those with the MYD88 L265P/CXCR4 WHIM genotype, and 80% versus 21% among those with the MYD88 WT/CXCR4 WT genotype ($n = 67$ MYD88 L265P/CXCR4 WT, HR 0.17, 95% CI 0.06–0.49; $p < 0.001$; $n = 49$ MYD88 L265P/CXCR4 WHIM, HR 0.24, 95% CI 0.09–0.66; $p < 0.001$; $n = 20$ MYD88 WT/CXCR4 WT, HR 0.21, 95% CI 0.04–1.08; $p < 0.001$). The 30-month PFS rates were 93% versus 22%, 70% versus 28%, and 86% versus 42% for patients of high, intermediate, and low prognostic scores, respectively ($n = 32$ low, HR 0.16, 95% CI 0.03–0.76; $p < 0.001$; $n = 61$ intermediate, HR 0.43, 95% CI 0.19–1.00; $p < 0.001$; $n = 57$ high, HR 0.07, 95% CI 0.02–0.31; $p < 0.001$).

D0005: How does ibrutinib affect symptoms and findings (severity, frequency) of Waldenström's macroglobulinemia?

ORR ITT:
ibrutinib combination: 92%
placebo combination: 47%

The secondary endpoint of BICR-assessed ORR in the ITT population was 92% in the ibrutinib combination group and 47% in the placebo combination group ($p < 0.0001$). Major response (MR), involving complete response (CR), very good partial response (VGPR) (≥90% reduction in serum IgM levels), or partial response (PR), was noted in 72% of ibrutinib combination versus 32% of placebo combination participants ($p < 0.0001$). A very good partial response was reported in 23% of ibrutinib combination versus 4% of placebo combination patients.

MYD88 L265P/CXCR WT or MYD88 L265P/CXCR4 WHIM genotypes had greater ORR than MYD88 WT/CXCR4 WT patients

Patients with MYD88 L265P/CXCR WT or MYD88 L265P/CXCR4 WHIM genotypes exhibited higher ORR than those with MYD88 WT/CXCR4 WT genotype. The ORR rates were 94% versus 46% among patients with the MYD88 L265P/CXCR4 WT genotype (n = 67), 100% versus 52% among those with the MYD88 L265P/CXCR4 WHIM genotype (n = 49), and 81% versus 55% among those with the MYD88 WT/CXCR4 WT genotype (n = 20) for the ibrutinib/rituximab arm versus the placebo/rituximab arm.

median DOR: not reached for ibrutinib combination vs. 21.2 months for placebo combination patients

Among those patients with partial or greater response, 92% of ibrutinib combination responders and 41% of placebo combination responders exhibited ongoing response at 24 months. The median DOR was not reached (range 1.9–36.4 months) among 54 patients with at least a partial response in the ibrutinib combination group and was 21.2 months (range 4.6–25.8) among 24 patients with partial or greater response in the placebo combination group.

IgM flare:
ibrutinib combination: 8%
placebo combination: 47%

After four weeks, the median IgM level was reduced from baseline by 56% with ibrutinib combination compared with an increase of 6% with placebo combination. Transient increases in IgM levels or flares were reported in 8% of the ibrutinib combination group and 47% of the placebo combination group. While 12 patients required plasmapheresis during the course of treatment, none were from the ibrutinib combination group.

increase in Hb:
ibrutinib combination: 73%
placebo combination: 41%

In the ITT population, the rate of sustained increase in Hb was 73% in the ibrutinib combination group and 41% in the placebo combination group ($p < 0.0001$), while that in of patients with anaemia at baseline was 95% and 56% ($p < 0.0001$), respectively.

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

atrial fibrillation, infection, hepatitis B reactivation, tumour lysis syndrome, hypertension, cytopenias

Ibrutinib may cause atrial fibrillation, infection, hepatitis B reactivation, fever, tumour lysis syndrome, and new onset hypertension or hypertension that is not adequately controlled. Based on a pooled safety analysis, ibrutinib may cause grade ≥3 cytopenias, including neutropenia (14%), thrombocytopenia (7%), and anaemia (6%) [4]. Patients should be monitored periodically for serum creatinine levels, and monthly for complete blood counts and symptoms of atrial fibrillation [4].

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

FACT-An: improvement from baseline

An improvement from baseline in the total score on the FACT-An was reported in 73% of ibrutinib combination patients and 59% of placebo combination patients ($p = 0.06$). Similarly 64% of ibrutinib combination and 48%

of placebo combination patients experienced an improvement in anaemia subscale score (p = 0.05).

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

No evidence reported regarding the effect of ibrutinib on disease-specific QoL.

disease-specific QoL: no evidence

Table 1: Efficacy results of iNNOVATE [7, 30]

Descriptive statistics and estimate variability	Treatment group	Ibrutinib + rituximab (n = 75)	Pl
	BICR-assessed 30 m OS, n (%)	71 (94)	
	BICR-assessed median 30 m PFS, m (95% CI) 24 m PFS rate, n (%) treatment-naïve (n = 68) 24 m PFS rate, n (%) relapsed disease (n = 82) 30 m PFS rate, n (%) MYD88 L265P/CXCR4WT (n = 67) 30 m PFS rate, n (%) MYD88 L265P/CXCR4WHIM (n = 49) 30 m PFS rate, n (%) MYD88WT/CXCR4WT (n = 20) 30 m PFS rate, n (%) high risk IPSSWM (n = 57) 30 m PFS rate, n (%) intermediate risk IPSSWM (n = 61) 30 m PFS rate, n (%) low risk IPSSWM (n = 32)	NA 29/34 (84) 33/41 (80) 28/32 (86) 21/26 (80) 9/11 (80) 25/27 (93) 23/33 (70) 13/15 (86)	
	BICR-assessed ORR, n, % (95% CI) CR, n (%) MYD88 L265P/CXCR4WT (n = 67) VGPR, n (%) MYD88 L265P/CXCR4WT (n = 67) CR, n (%)MYD88 L265P/CXCR4WHIM (n = 49) VGPR, n (%)MYD88 L265P/CXCR4WHIM (n = 49) CR, n (%)MYD88WT/CXCR4WT (n = 20) VGPR, n (%)MYD88WT/CXCR4WT (n = 20)	69 (92), p < 0.001 2/32 (6) 9/32 (28) 0/26 (0) 5/26 (19) 0/11 (0) 3/11 (27)	
	BICR-assessed median DOR, n, m (range) (n = 78)	n = 54 NA (1.9–36.4)	n =
	IgM flare, n (%)	6 (8)	
	Sustained increase in Hb, n (%)	55 (73), p<0.001	
	FACT-An (%)	73, p = 0.06	
Effect estimate per comparison	*Comparison groups*	Ibrutinib combination versus pla	
	BICR-assessed PFS (n = 150) (primary endpoint)	HR	
		95% CI	
		Log-rank test p-value	
	PFS, treatment-naive (subgroup analysis, n = 68)	HR	
		95% CI	
		Log-rank test p-value	
	PFS, relapsed disease (subgroup analysis, n = 82)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, (%) MYD88 L265P/CXCR4WT (subgroup analysis, n = 67)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, MYD88 L265P/CXCR4WHIM (subgroup analysis, n = 49)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, MYD88WT/CXCR4WT (subgroup analysis, n = 20)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, low risk IPSSWM (subgroup analysis, n = 32)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, intermediate risk IPSSWM (subgroup analysis, n = 61)	HR	
		95% CI	
		Log-rank test p-value	
	30 m PFS rate, high risk IPSSWM (subgroup analysis, n = 57)	HR	
		95% CI	
		Log-rank test p-value	

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DOR = duration o Functional Assessment of Cancer Therapy-Anaemia; Hb = haemoglobin; HR = hazard ratio; m = months; n = number; NA = reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; VGPR = very g = wild type

7.2.2 Safety

C0008: How safe is ibrutinib in relation to the comparator(s)?

In the safety population (n = 150), investigator-assessed AEs were more commonly reported in the ibrutinib- than placebo combination groups, respectively, included diarrhoea (28% versus 15%), arthralgia (24% versus 11%), and nausea (21% versus 12%). In contrast, IgM flare (8% versus 47%), infusion-related reactions (43% versus 59%), fatigue (13% versus 27%), asthenia (16% versus 25%), anaemia (19% versus 29%), and headache (13% versus 23%) were less commonly reported in the ibrutinib- than placebo combination group.

common AEs: diarrhoea, arthralgia and nausea

Approximately 60% of patients in each group experienced at least one AE of ≥3 severity. Hypertension (13% versus 4%) and atrial fibrillation (12% versus 1%) were more frequent in those receiving ibrutinib combination, while anaemia (11% versus 17%) and infusion reactions (1% versus 16%) were more common in those receiving placebo combination. Pneumonia (8%), atrial fibrillation (7%) and respiratory tract infection (4%) were the most common serious AEs observed with ibrutinib combination. Fatal AEs occurred in no patients in the ibrutinib combination group and three patients in the placebo combination group.

common grade ≥ 3 AEs: hypertension and atrial fibrillation

serious AEs: pneumonia, atrial fibrillation and respiratory tract infection

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

Median DOT was 25.8 months (range 1.0–37.2) for ibrutinib combination and 15.5 months (range 0.4–34.3) for placebo combination. AEs of grade ≥3 severity were observed in 60% and 61% of patients in the ibrutinib- and placebo combination groups, respectively. Approximately 5% of ibrutinib combination patients and 4% of placebo combination patients discontinued due to AEs. AEs led to a dose reduction in 13 (1%) ibrutinib combination patients, most commonly as a result of neutropenia (n = 3), atrial fibrillation (n = 2), and muscle spasm (n = 2).

5% discontinued due to AEs; 1% reduced dose for neutropenia, atrial fibrillation or muscle spasm

Atrial fibrillation, of any grade, occurred in 15% of ibrutinib- and 3% of placebo combination patients. Among those with atrial fibrillation, a history of atrial fibrillation was reported in 27% of those in the ibrutinib combination group and none of those in the placebo combination group.

atrial fibrillation: 15% for ibrutinib combination versus 3% for placebo combination

Bleeding events were more common in patients treated with ibrutinib- than placebo combination (51% versus 21%); grade 1 or 2 events occurred in 92% versus 81% of patients, respectively. Major haemorrhage was reported in three (4%) patients in each treatment group. The use of anticoagulant or antiplatelet medications was more common with ibrutinib combination than placebo combination (43% versus 36%), respectively. One placebo combination patient experienced a fatal intracranial haemorrhage.

bleeding: 51% for ibrutinib combination versus 21% for placebo combination

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

susceptibles: elderly; history of atrial fibrillation, hepatic impairment, anticoagulants or platelet inhibitors

Ibrutinib is generally avoided in patients with a history of arrhythmia, significant hepatic impairment, severe bleeding, and in those on anticoagulation [4, 35]. Study participants had a median age of 69 years (range 36–89), with good performance status (ECOG 0–1). Patients with a history of stroke, intracranial haemorrhage, CNS involvement, bleeding disorders, systemic infection or cardiovascular disease were excluded from study. Approximately 55% of atrial fibrillation observed in the ibrutinib combination group, was reported in patients aged 75 years of age or older [29].

common AEs in elderly: thrombocytopenia, pneumonia, urinary tract infection, hypertension, atrial fibrillation, and hyponatraemia

In pooled safety analysis, AEs of grade ≥3 severity were more frequent among patients aged 65 years of age and older than younger patients (73% versus 66%, respectively), as were AEs leading to discontinuation (14% versus 8%, respectively) and fatal AEs (8% versus 4%, respectively) [4]. Events more commonly reported in patients 65 years of age and older compared with younger patients included thrombocytopenia, pneumonia, urinary tract infection, hypertension, atrial fibrillation, and hyponatraemia [4].

ibrutinib may cause foetal harm; hold pre- and post-operatively

Ibrutinib may cause foetal harm and potential for serious AEs in nursing infants. Females are advised to use highly effective contraceptives and to discontinue breastfeeding during ibrutinib treatment. Males are advised not to father a child while receiving ibrutinib, and for three months following completion of treatment [4]. Depending on the type and risk of bleeding, ibrutinib should be held three to seven days pre- and post-surgery.

: Most frequent adverse events [7, 29]

se Event (according CAE version 4.03)	**Ibrutinib-Rituximab** (n = 75)	**Placebo-Rituximab** (n = 75)
ommon AEs of any grade n (%)		
(%)	75 (100)	75 (100)
sion-related reaction	32 (43)	44 (59)
rrhoea	21 (28)	11 (15)
ralgia	18 (24)	8 (11)
sea	16 (21)	9 (12)
emia	14 (19)	22 (29)
ertension	14 (19)	4 (5)
enia	12 (16)	19 (25)
al fibrillation	11 (15)	2 (3)
gue	10 (13)	20 (27)
dache	10 (13)	17 (23)
flare	6 (8)	35 (47)
≥ 3 AEs n (%)	45 (60)	46 (61)
ertension	10 (13)	3 (4)
al fibrillation	9 (12)	1 (1)
emia	8 (11)	13 (17)
tropenia	7 (9)	2 (3)
umonia	7 (9)	2 (3)
onatremia	4 (5)	2 (3)
gue	2 (3)	1 (1)
sion-related reaction	1 (1)	12 (16)
ombocytopenia	0 (0)	4 (5)
enia	0 (0)	2 (3)
rrhoea	0 (0)	1 (1)
flare	0 (0)	2 (3)
s AEs n (%)	32 (43)	25 (33)
umonia	6 (8)	2 (3)
al fibrillation	5 (7)	1 (1)
piratory tract infection	3 (4)	0 (0)
emia	2 (3)	0 (0)
gestive cardiac failure	2 (3)	0 (0)
	2 (3)	0 (0)
troenteritis	2 (3)	0 (0)
cardial ischemia	2 (3)	0 (0)
ralgia	2 (3)	0 (0)

ations: AE = adverse event; CTCAE = common terminology for cancer adverse events; IgM = immunoglobulin M

7.3 Clinical effectiveness and safety – further studies

NCT01614821: ibrutinib monotherapy in 63 refractory WM patients

NCT01614821 is a multicentre, open-label, prospective, phase II study to evaluate the safety and efficacy of ibrutinib in 63 symptomatic patients with previously treated WM, and investigate the influence of MYD88 and CXCR4 mutations on outcomes [6]. Patients received 420 mg of ibrutinib orally once daily for twenty-six 4-week cycles until progression or unacceptable toxicity. The primary endpoint was BICR-assessed ORR, defined as the sum of minor responses (≥25% reduction in serum IgM levels), partial responses (≥50% reduction in serum IgM levels), very good partial responses (≥90% reduction in serum IgM levels), and complete responses (100% reduction in serum IgM levels). Responses were defined according to criteria adopted from the Third International Workshop on WM. The secondary endpoints were to determine PFS and safety. A total of 63 consecutive eligible patients contributed to the efficacy and safety population. The median DOT was 19.1 months (range 0.5–29.7); 43 (68%) patients continued therapy after the database was locked December 19, 2014.

cohort: 63 years of age, 76% male, 78% intermediate prognostic score

MYD88 L265P: 89% CXCR4 WHIM: 34%

The study population (n = 63) had a median age of 63 years (range 44–86), 76% were male, 78% had an intermediate or high prognostic score, median bone marrow (BM) involvement of 60% (range 3–95), and a median of 74 months since diagnosis. Patients with relapsed disease had received a median of two prior therapies (range 1–9); of these, 85% were previously treated with a monoclonal antibody. At baseline, the median serum IgM level was 3.5 g/dL (range 0.7–8.4). Of the 62 patients for whom baseline mutational data were available, 89% were MYD88 L265P and 34% were CXCR4 WHIM.

median serum IgM decrease: 2,640 mg/dL

Hb increase: 3.3 g/dL

ORR: 90.5%
PFS: 69.1%
OS: 95.2%

high IPSS, ≥ 3 previous treatments, and MYD 88 WT/CXCR4 WT associated with lower PFS

AEs: neutropenia, thrombocytopenia, post-procedural bleeding, epistaxis, atrial fibrillation

Median serum IgM levels decreased from 3,520 mg/dL to 880 mg/dL and Hb levels increased from 10.5 g/dL to 13.8 g/dL. BM involvement decreased from 60% to 25 % ($p < 0.01$). The median time to a minor response was four weeks. At a median DOT of 19.1 months (range 0.5–29.7), the ORR was 90.5% and the major response rate was 73.0%. Response was highest among patients with MYD88 L265P/CXCR4 WT (100.0% ORR and 91.2% major response rate), followed by MYD88 L265P/CXCR4 WHIM (85.7% and 61.9%, respectively), and patients with MYD88 WT/CXCR4 WT (71.4% and 28.6%, respectively). Estimated 2-year PFS and OS rates among all patients were 69.1% (95% CI 53.2–80.5) and 95.2% (95% CI 86.0–98.4), respectively. Among patients with progressive disease, the median time to progression was 9.6 months (range 3.5–19.4). Subgroup analysis suggests that a high IPSS score, greater than three previous treatment regimens, and a MYD88 WT/CXCR4 WT genotype were associated with lower rates of PFS. Treatment-related AE of grade ≥2 severity included neutropenia (22%) and thrombocytopenia (14%), which were more common in heavily pre-treated patients; post-procedural bleeding (3%); epistaxis associated with use of fish-oil supplements (3%); and atrial fibrillation associated with a history of arrhythmia (5%). AEs resulted in dose reductions in ten patients.

8 Estimated costs

A0021: What is the reimbursement status of ibrutinib?

€ 226,443.26 per patient for 25.8 months of ibrutinib + rituximab therapy

In Austria, ibrutinib is available in 90- and 120-capsule bottles of 140 mg capsules for € 5,474.70 and € 7,299.60, respectively [23]. At the recommended dosage of 420 mg (three 140 mg capsules) per day, a median duration of treatment of 25.8 months would cost approximately € 141,247.26. Ibrutinib therapy is administered in combination with two four-week courses of rituximab (375 mg/m^2 IV) every five months, at an additional cost of approximately € 85,196.00 per median duration of treatment of 25.8 months [31]. Overall, it would cost approximately € 226,443.26 to treat each WM patient with ibrutinib in combination with rituximab. Since close to 26 patients are diagnosed with WM in Austria annually [23], and approximately 91% have MDY88 L265P mutations that could benefit from therapy [6], ibrutinib in combination with rituximab would cost approximately € 5,357,647.50 per year. Additional costs to assess the mutational status of MYD88 and CXCR4 will incur.

9 Ongoing research

14 registered studies

A few studies are ongoing to investigate ibrutinib as monotherapy or in combination with other targeted therapies for treatment naïve WM and those with relapsed disease. In November 2018, searches of www.clinicaltrials.gov and www.clinicaltrialsregister.eu using the search terms "ibrutinib" and "Waldenstrom Macroglobulinemia" yielded 14 other registered studies (two phase III, six phase II, one phase I/II, and five phase I studies). Most studies were industry-sponsored or conducted in collaboration with industry.

9 phase II/III studies

Selected ongoing phase III, II, II/I, and I studies evaluating ibrutinib in combination with rituximab and bendamustine, or pembrolizumab for relapsed or refractory WM, versus zanubrutinib for WM, in hepatitis B carriers with relapsed or refractory WM, in previously untreated WM in relation to tumour genomic evolution, in combination with daratumumab, as first-line with bortezomib and rituximab for WM, in combination with ulocuplumab in WM patients with CXCR4 mutations, and in combination with ixazomib for relapsed or refractory disease:

- **NCT01479842:** is a phase I, open-label, single-group, interventional study to evaluate the activity of combined rituximab, bendamustine, and ibrutinib in patients with relapsed and refractory B-cell NHL, including WM. Estimated study completion date is December 2018.
- **NCT02332980:** is a phase II, open-label, single-group, interventional study to explore the efficacy of pembrolizumab alone or in combination with idelalisib or ibrutinib for patients with low-grade B-

cell non-Hodgkin lymphomas, including WM. Estimated study completion date is January 2020.

- **NCT03053440:** is a phase III, randomised, open-label, multicentre study comparing the safety and efficacy of the BTK inhibitors zanubrutinib and ibrutinib in patients with WM. Estimated study completion date is June 2021.
- **NCT02991638:** is a phase III, randomised, open-label, interventional study to assess the safety and efficacy of ibrutinib in hepatitis B carriers with relapsed/refractory lymphocytic leukaemia or WM Estimated study completion date is June 2021.
- **NCT02604511:** is a phase II, open-label, single-group, interventional study to investigate the safety and efficacy of ibrutinib in untreated WM patients and to identify genetic changes that effect how ibrutinib works using genomic sequencing. Estimated study completion date is February 2023.
- **NCT03679624:** is a phase II, non-randomised, open-label, cohort study to evaluate the effectiveness of adding daratumumab to ibrutinib for WM. Estimated study completion date is November 2023.
- **NCT03620903:** is a phase II, open-label, single-group, interventional study to assess the toxicity and efficacy of bortezomib, rituximab and ibrutinib (B-RI) for treatment-naïve WM. Estimated study completion date is November 2024.
- **NCT03225716:** is a phase I/II, open-label, single-group, interventional study to evaluate the safety, dosage, and ORR of ulocuplumab and ibrutinib in symptomatic patients with mutated CXCR4 WM. Estimated study completion date is January 2025.
- **NCT03506373:** is a phase II, open-label, single-group, interventional study to explore the effectiveness of ibrutinib in combination with ixazomib for relapsed or refractory WM. Estimated study completion date is May 2025.

10 Discussion

FDA and EMA: monotherapy for WM

FDA: expanded approval in combination with rituximab as any-line

EMA: currently no MAA to extend use in combination with rituximab for WM

In January 2015, both the FDA and the EMA licensed ibrutinib as monotherapy for the treatment of relapsed or refractory WM, or as first-line therapy for patients unsuitable for immunochemotherapy [13]. Approval was based on the ORR reported in a phase II multicentre cohort study [6]. In August 2018, the FDA approval was expanded to include combination use with rituximab across all lines of therapy for WM based on 30-month PFS rates reported in the phase III iNNOVATE trial [7, 8]. There is no indication as to when the EMA may receive a MAA to extend the use of ibrutinib in combination with rituximab for WM. Ibrutinib is also currently approved by the FDA and EMA for use as second-line for MCL, any-line monotherapy for CLL, second-line in combination with bendamustine and rituximab for CLL and SLL, and GVHD [4, 14].

iNNOVATE

iNNOVATE, a double-blind, randomised, phase III study investigated whether adding ibrutinib to rituximab prolongs PFS and ORR in 150 symptomatic WM patients, 68 of whom had disease recurrence [7]. Stratified by prognostic score, number of prior treatments and ECOG status, participants were randomised 1:1 to 420 mg oral ibrutinib or placebo until disease progression or toxicity. Patients also received 375 mg/m^2 rituximab IV once weekly for four weeks, followed by another four-week course after a three-month interval. Adding ibrutinib prolonged PFS by 54%, conferring a longer PFS than rituximab alone at 26.5 months (not reached versus 20.3 months, respectively) and reducing the relative risk of progression or death by 80%. The PFS benefit was observed regardless of previous treatment, MYD88 or CXCR4 genotype, or prognostic score. At 30 months, the OS rates were 94% versus 92% for ibrutinib- and placebo combination, respectively; median OS was not reached in either group. Adding ibrutinib to rituximab increased the ORR by 45% compared with rituximab alone with robust response rates across all genotypes. Adding ibrutinib to rituximab therapy increased the number of patients with sustained Hb by 32% and resulted in fewer IgM flares (8% versus 47%, respectively). Ibrutinib combination increased the FACT-An by 14% and the anaemia subscale score by 16%.

PFS: ibrutinib increased PFS by 54%, reduced risk of progression or death regardless of prior treatment, genotype or prognostic score

immature OS

Commonly reported AEs in ibrutinib combination patients compared to rituximab alone included diarrhoea, arthralgia, and nausea. Hypertension and atrial fibrillation were the most common AEs of grade ≥3 severity. The most common serious AEs observed with ibrutinib combination include pneumonia (8%), atrial fibrillation (7%), and respiratory tract infection (4%). AEs led to a dose reduction in 13 ibrutinib combination recipients, most commonly as a result of neutropenia, atrial fibrillation, or muscle spasm. Atrial fibrillation and bleeding events were 12% and 30% more common in the ibrutinib combination versus rituximab alone.

increased number of patients with sustained Hb; reduced IgM flares

common serious or severe AEs: pneumonia, atrial fibrillation, hypertension, bleeding, and respiratory tract infection

The results of iNNOVATE hold some limitations. Follow-up is insufficient to evaluate OS and long-term safety. No evidence was reported regarding the effect of ibrutinib combination on disease-specific QoL. Mature OS data and disease-specific QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity. The large confidence intervals associated with some subgroup analyses such as that for PFS of MYD88 WT/CXCR4 WT, or low prognostic score suggest a larger sample size would be needed to gain greater precision regarding the effect of these factors on outcomes.

iNNOVATE limitations: lack of data regarding OS, QoL, precision, and biomarkers predictive of response

Generalizability may be limited in that the study population had good performance status (ECOG ≤1: n = 140/150), those with relapsed disease received a median of two prior therapies, and of these, were rituximab sensitive. Patients with CNS involvement, cardiovascular disease, bleeding disorders, infections, stroke or intracranial haemorrhage were excluded from study. The applicability of these study results for patients with higher ECOG performance status, cardiac risk factors, hypertension, bleeding, or rituximab resistance needs further evaluation. While MYD88 and CXCR4 mutation status influenced response to ibrutinib, other biomarkers warrant further investigation in defining possible responders to treatment. While rituximab is a suitable comparator, bendamustine and rituximab may also be appropriate as first-line therapy, bortezomib-rituximab-dexamethasone is suitable for those with symptomatic hyperviscosity, and ofatumumab is appropriate for previously-treated WM intolerant to rituximab. Without direct comparison trials, physicians and patients may need to discuss whether add-

limited generalizability of results to patients with higher ECOG status, cardiac risk factors, or rituximab resistance

ing ibrutinib to rituximab would provide greater individualised efficacy than ibrutinib monotherapy.

low risk of bias: randomised, double-blind, comparator-matched

however, industry funded, cross-over

iNNOVATE is a phase III trial with few methodological limitations. There was no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 1:1 to ibrutinib combination or placebo combination using a web-based response system [5]. Patients, physicians, and outcome assessors were blinded as patients received ibrutinib or matching placebo on an outpatient basis. Selective reporting is unlikely as the primary endpoint of PFS, secondary endpoints of OS, ORR, Hb TTNT, QoL and safety were reported as specified in the protocol. The risk of bias may be increased by cross-over (30 patients switched to ibrutinib monotherapy after progression), and industry involvement in funding the study, collecting, confirming and compiling data for analysis, and drafting and reviewing the manuscript.

consistent efficacy and safety results compared with phase II study

while MYD88 and CXCR4 mutations influenced response to ibrutinib monotherapy, responses to ibrutinib combination were similar across genotypes but lower among MD88 WT

The efficacy and safety data from iNNOVATE are consistent with a previously reported phase II study suggesting ibrutinib monotherapy reduces serum IgM, increases Hb, and confers ORR, PFS and OS rates in the range of 90.5%, 69.1%, and 95.2%, respectively, in refractory WM patients [6]. While IPSSWM risk factors were developed to predict OS, increased PFS was observed across prognostic scores in the iNNOVATE trial. In the previous phase II study, mutations in MYD88 and CXCR4 influenced response to ibrutinib monotherapy, whereas response rates with ibrutinib combination were similar across different CXCR4 genotypes but lower among patients lacking the activating MYD88 L265P mutation. While minor differences in response rates with regards to the MYD88/CXCR4 genotypes did not affect the PFS benefit observed with ibrutinib combination, authors recommend exercising caution due to small sample size. Rates of atrial fibrillation with ibrutinib combination were similar to those reported in long-term follow-up for ibrutinib monotherapy.

ongoing studies evaluating ibrutinib as monotherapy or in combination with pembrolizumab, daratumumab, ixazomib, ulocuplumab, or rituximab and bendamustine

A few studies are underway to investigate ibrutinib as monotherapy or in combination with other targeted therapies for symptomatic untreated WM and those with relapsed disease. Ongoing phase III studies are evaluating the comparative effectiveness of zanubrutinib versus ibrutinib for WM, and the efficacy of ibrutinib in hepatitis B carriers with refractory WM. Phase II studies are investigating the efficacy of pembrolizumab alone or in combination with idelalisib or ibrutinib; the addition of daratumumab to ibrutinib for WM; ibrutinib in combination with ixazomib for refractory disease; and the genetic changes that affect the efficacy of ibrutinib in untreated WM. Phase I studies are exploring the activity of combined rituximab, bendamustine and ibrutinib in WM, and the safety and ORR of ulocuplumab and ibrutinib in symptomatic patients with mutated CXCR4 WM.

€ 226,443.26 per patient for 25.8 months of ibrutinib + rituximab therapy

At the recommended dosage of 420 mg (three 140 mg capsules) of ibrutinib per day, a median DOT of 25.8 months would cost approximately € 141,247.26 [23]. Ibrutinib therapy is administered in combination with two four-week courses of rituximab (375 mg/m^2 IV) every five months, at an additional cost of approximately € 85,196.00 per median DOT of 25.8 months [31]. Overall, it would cost approximately € 226,443.26 to treat each WM patient with ibrutinib in combination with rituximab. Since close to 26 patients are diagnosed with WM in Austria annually [23], and approximately 91% have MDY88 L265P mutations that could benefit from therapy [6], ibrutinib in combination with rituximab would cost approximately €

5,357,647.50 per year. Additional costs to assess the mutational status of MYD88 and CXCR4 will incur.

development of more specific inhibitors: zanubrutinib, ONO/GS-4059, acalabrutinib, and vecabrutinib to reduce AEs and treatment discontinuation

a combination may be required to maintain remission

Ibrutinib-related AEs result from binding to other tyrosine-protein kinases (TEC) and epidermal growth factor receptors (EGFR). There is uncertainty as to which side effects are due to on-target BTK inhibition in nonlymphoma tissues versus off-target kinase inhibition. There is evidence of higher BTK/TEC expression in the myocardium of AF patients versus those with sinus rhythm, and ibrutinib inhibits the transduction of cardioprotective PI3K/AKT signalling. AEs and the development of ibrutinib resistance have led to the development of more specific BTK inhibitors, such as zanubrutinib (BGB-3111), ONO/GS-4059, acalabrutinib (ACP-196), and vecabrutinib (SNS-062). Approximately 50% of WM patients that progress on ibrutinib acquire new mutations on cysteine 481 of the BTK gene that abrogate binding of the drug to the protein while mediating cell survival through sustained ERK phosphorylation and pro-inflammatory cytokine secretion. Given the need for indefinite continuous treatment, fewer AEs may reduce discontinuation and prolong PFS for WM patients. While new inhibitors, like CXCR4-blocking antibody vecabrutinib may overcome acquired BTK C481S-induced ibrutinib resistance, it would not overcome PLCγ2-induced and ARD11-mutation-induced resistance. It is unclear whether any new BTK inhibitor can induce complete remission in WM patient; ibrutinib in synergistic combination with IRAK, SYK or Src kinase inhibitors may be more potent. A combinatorial approach could target different aspects of cell biology resulting in superior clinical response compared with BTK inhibitor monotherapy [2].

iNNOVATE: phase III RCT demonstrates PFS and ORR benefit of ibrutinib combination over rituximab alone

optimal therapeutic sequence, monotherapy versus in combination, comparison with new BTK inhibitors remains unknown

Overall, iNNOVATE is the first phase III, randomised, double-blind study to demonstrate that adding ibrutinib to rituximab therapy increases PFS and ORR in symptomatic untreated WM and those with relapsed/refractory disease. The PFS and ORR benefits of ibrutinib combination over rituximab alone were consistent across subgroups regardless of line, genotype or prognostic score. Adding ibrutinib to rituximab therapy increased the number of patients with sustained Hb and reduced IgM flares. Data regarding OS is needed to ensure patients derive a clinically relevant benefit over time despite manageable toxicity. However, it is very unlikely that this study is appropriate to demonstrate a potential OS benefit because of the possibility of crossover to ibrutinib for patients with progression upon rituximab/placebo treatment. Biomarkers would ensure the appropriate selection of patients most likely to benefit from treatment. Further evaluation is needed to identify the role of ibrutinib as first-line versus salvage therapy; monotherapy versus in combination with biologic agents, other small molecules or chemoimmunotherapy; optimal duration of treatment; management of ibrutinib intolerant or resistant patients; and the comparative safety and effectiveness with new BTK inhibitors.

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12 Appendix

Table 3: Administration and dosing and of ibrutinib or placebo + rituximab [4, 5, 7, 14]

	Ibrutinib + rituximab	Placebo + rituximab
Administration mode	Swallow oral capsules whole with 8 ounces of water, with or without food, once daily at approximately the same time each day [4].	Matching placebo [7]
Description of packaging	140 mg white capsules marked "ibr 140 mg" in black ink packaged in HDPE bottles of 90 or 120 capsules [4]; 4-week blister packs of 140 mg, 280 mg, 420 mg and 560 mg film-coated tablets [14]	Matching placebo [7]
Total volume contained in packaging for sale	90- and 120-capsule bottles of 140 mg capsules contain 90 and 120 capsules, respectively (140 mg per capsule, 3 x 140 mg capsules once daily [4];	Matching placebo [7]
Dosing	420 mg ibrutinib (3 x 140 mg capsules) once daily until progression or unacceptable toxicity [4]; dosed 0-30 minutes before rituximab infusion on week 4. Patients received rituximab (375 mg/m² IV at weeks 1-4 and 17-20) [5]. Withhold for grade ≥3 non-haematological toxicities, grade ≥3 neutropenia with infection or fever, or grade 4 haematological toxicities; resume once symptoms resolve to grade 1 or baseline. If toxicity reoccurs, reduce dose by one capsule (140 mg/day). Discontinue if toxicities persist or recur following two dose reductions [4].	Matching placebo, identical administration. Patients received rituximab (375 mg/m² IV at weeks 1-4 and 17-20) [5]. Withhold for grade ≥3 non-haematological toxicities, grade ≥3 neutropenia with infection or fever, or grade 4 haematological toxicities; resume once symptoms resolve to grade 1 or baseline. If toxicity reoccurs, reduce dose by one capsule (140 mg/day). Discontinue if toxicities persist or recur following two dose reductions [4].
Median treatment duration, m (range)	Until progression or unacceptable toxicity; median DOT: 25.8 months (1.0-37.2)	Until progression or unacceptable toxicity; cross-over to ibrutinib permitted after BIRC-assessed progression; median DOT: 15.5 months (0.4-34.4)
Contraindications	Not for use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). Reduce dose to 140 mg in patients with mild hepatic impairment [4].	Not for use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). Reduce dose to 140 mg in patients with mild hepatic impairment [4].
Drug interactions	Avoid CYP3A inhibitors/inducers, grapefruit and Seville oranges. Hold or reduce dose to 140 mg ibrutinib for duration of strong or moderate CYP3A treatment. Take digoxin ≥6 hours before or after ibrutinib; monitor ECG and electrolytes when using medications that prolongs QT. Caution in subjects on anticoagulants or platelet inhibitors [4].	Matching placebo [7]

Abbreviations: BIRC = blinded independent review committee; DOT = duration of treatment; ECG = electrocardiogram; HDPE = high-density polyethylene; IV = intravenous

Table 4: Characteristics of the iNNOVATE trial [7]

Title: Ibrutinib with rituximab in adults with WM (iNNOVATE) [5, 7, 30]			
Study identifier	NCT02165397, EUDRACT2013-005478-22, PCYC-1127-CA, iNNOVATE		
Design	International (9 countries), multicentre (45 sites), randomised, double-blind, interventional phase III		
	Duration of treatment phase:		July 2014 – January 2016, time from randomisation to end of treatment visit (30 days from last day of study treatment or prior a new anticancer treatment). Treatment occurs within 72 hours of randomisation. Data from interim analysis at 30 months.
	Duration of screening phase:		30 days prior to study treatment; subjects meeting inclusion criteria are eligible for study
	Duration of extension phase:		After end-of-treatment visit, subjects are monitored every 12 weeks through response follow-up or survival follow-up until death, loss to follow-up, consent withdrawal, or study end.
Hypothesis	Superiority The primary hypothesis is that ibrutinib in combination with rituximab will result in an improvement in PFS compared to placebo in combination with rituximab in subjects with symptomatic WM.		
Funding	Pharmacyclics and Janssen Research and Development		
Treatments groups	Ibrutinib + rituximab (Arm A, RCT) (n = 75 efficacy; n = 75 safety)		Ibrutinib: 420 mg (3 oral capsules x 140 mg) administered daily beginning from day 1 Rituximab: 375 mg/m² IV once weekly for four consecutive weeks (weeks 1-4), followed by a second four-weekly rituximab course after a three-month interval (weeks 17-20).
	Placebo + rituximab (Arm B, RCT) (n = 75 efficacy; n = 75 safety)		Placebo: 3 matching oral capsules administered daily beginning from day 1 Rituximab: 375 mg/m² IV once weekly for four consecutive weeks (weeks 1-4), followed by a second four-weekly rituximab course after a three-month interval (weeks 17-20).
	Ibrutinib (Arm C, open label sub-study) (n = NR efficacy; n = NR safety)		Ibrutinib: 420 mg (3 oral capsules) administered daily beginning from day 1
	Notes		MYD88 and CXCR4 mutation status was assessed in bone marrow samples prior to starting treatment. Treatment continued until progression or unacceptable toxicity. Placebo + rituximab patients were permitted to cross-over to receive ibrutinib after BIRC-assessed progression (n = 30). Since treatment-naïve patients were enrolled after a protocol amendment, 30 m PFS rates could not be estimated among these patients.
Endpoints and definitions	Progression-free survival Primary endpoint	PFS	Time from randomisation until progression or death (up to 3 years), as assessed by BICR, based on the modified Consensus Response Criteria from the VIth IWWM (NCCN 2014)
	Overall survival Secondary endpoint	OS	Time from randomisation until all-cause death up to 3 years
	Overall response rate Secondary endpoint	ORR	Number (%) of patients with confirmed CR or PR, as assessed by BIRC, based on the modified VIth IWWM (NCCN 2014) criteria
	Haematological improvement Secondary endpoint	Hb	Number (%) of patients with sustained HgB improvement, as measured by an increase from baseline ≥ 2 g/dL or for patients with baseline anaemia, an increase to a HgB >11 g/dL for ≥ 56 days without transfusion or growth factors
	Time to next treatment Secondary endpoint	TTNT	Time from randomisation to start date of any subsequent WM treatment (up to 3 years)
	Quality of life Secondary endpoint	QoL	Proportion of subjects with ≥ 3 points increase from baseline by week 25 in the FACIT-Fatigue subscale score. FACT-An total score and anaemia subscale score; clinically meaningful improvement defined as an increase of ≥ 7 points in FACT-An total score and ≥ 6 points in anaemia subscale score.
	Adverse events Secondary endpoint	AEs	AEs graded by CTCAE version 4.03, up to 30 days following last dose of study drug

Title: Ibrutinib with rituximab in adults with WM (iNNOVATE) [5, 7, 30]			
Study identifier	NCT02165397, EUDRACT2013-005478-22, PCYC-1127-CA, iNNOVATE		
	Investigator-assessed PFS Investigator-assessed ORR Duration of response Clinical response rate Minor response Medical resource utilization Immunoglobulin M Bone marrow tumour Lymph and spleen function Exploratory endpoints	PFS ORR DOR CRR MR MRU IgM — —	Investigator-assessed progression-free survival Investigator-assessed overall response rate Time of response to until BICR-assessed progression or death Number (%) achieve ≥ minor response Criteria from the VIth IWWM (NCCN 2014) Plasmapheresis, blood transfusions, growth factors Median immunoglobulin M Presence of bone marrow tumour Function of lymph and spleen
Database lock	Last update posted May 8, 2018		
Results and Analysis			
Analysis description	**Primary Analysis** ITT: efficacy analyses included all patients randomised. Safety analysis included all patients who received at least one dose of study drug (rituximab, ibrutinib/placebo). Primary analysis for PFS was a 2-sided log-rank test stratified according to IPSSWM (low, intermediate, high) and number of prior regimens (0, ≥ 1). Alpha spending for PFS was determined based on the actual information fraction using the O'Brien-Fleming boundary. Kaplan-Meier was used to estimate the PFS distribution; HR for ibrutinib versus placebo and associated 95% CI was calculated based on the stratified Cox proportional hazards model. Subgroup analyses of PFS are based on an un-stratified Cox model. Secondary end points were tested at the 2-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure. ORR and haematological improvement were compared using the stratified Cochran-Mantel-Haenszel chi-square test. TTNT was analysed using stratified or un-stratified log-rank as appropriate. OS analysed using stratified log-rank. OS and median OS distribution with 95% CI were estimated using the Kaplan-Meier product-limit method. A target HR for progression or death of 0.50, with 71 events provided a power of 80% based on 2-sided log-rank test at an alpha of 0.5. Study results represent the pre-interim analysis planned after approximately 60% (n = 42) events of BICR-assessed progression or death. Final PFS analysis is scheduled following approximately 70 BICR-assessed events.		
Analysis population	Inclusion (Arms A & B, RCT)		✪ Untreated or previously treated WM; previously treated subjects must have documented progression or no response to recent treatment. ✪ Centrally confirmed diagnosis of WM ✪ Measurable disease defined as serum monoclonal IgM >0.5 g/dl ✪ Symptomatic disease meeting ≥ 1 recommendations from the 2nd IWWM for requiring treatment ✪ Haematology and biochemical values within protocol-defined limits ✪ Men and women ≥ 18 years of age ✪ EGOG performance status ≤ 2

Title: Ibrutinib with rituximab in adults with WM (iNNOVATE) [5, 7, 30]				
Study identifier	NCT02165397, EUDRACT2013-005478-22, PCYC-1127-CA, iNNOVATE			
	Exclusion	✪ Known CNS involvement ✪ Rituximab-resistant disease, defined as: relapse after last rituximab-containing therapy <12 months since last dose, or failure to achieve a MR after the last rituximab-containing therapy. If the subject meets this exclusion criterion and is excluded from the main randomized study, participation in the non-randomized sub-study (Arm C) may be considered. ✪ Rituximab treatment within 12 months of first dose of study drug ✪ Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or component of rituximab ✪ Prior exposure to ibrutinib or other BTK inhibitors ✪ Known bleeding disorders (e.g., von Willebrand's disease) or haemophilia ✪ History of stroke or intracranial haemorrhage within 12 months prior to enrolment ✪ Any uncontrolled active system infection ✪ Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion could compromise the subject's safety or put the study outcomes at undue risk ✪ Currently active, clinically significant CVD ✪ Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor		
	Inclusion (Arm C, open-label sub-study)	✪ Identical to those of the randomised study, but subjects need to be considered refractory to the last prior rituximab-containing therapy defined as either: relapse after the last rituximab-containing therapy <12 months since last dose of rituximab, or failure to achieve at least a MR after last rituximab-containing therapy.		
	Characteristics	Ibrutinib-Rituximab (n = 75)	Placebo-Rituximab (n = 75)	Total (n = 150)
	Age Median age (range), years ≥ 75 years, n (%)	 70 (36-89) 30 (40)	 68 (39-85) 20 (27)	 69 (36-89) 50 (33)
	Male, n (%)	45 (60)	54 (72)	99 (66)
	Median time from diagnosis (range), months	50 (1–257)	56 (1–247)	53 (1–257)
	ECOG performance-status, n (%) 0 1 2	 39 (52) 32 (43) 4 (5)	 37 (49) 32 (43) 6 (8)	 76 (51) 64 (43) 10 (7)
	Prognostic score, n (%) Low Intermediate High	 15 (20) 33 (44) 27 (36)	 17 (23) 28 (37) 30 (40)	 32 (21) 61 (41) 57 (38)
	Genotype, n/N (%) MYD88WT/CXCR4 WT MYD88L265P/CXCR4 WT MYD88L265P/CXCR4 WHIM	 11/69 (16) 32/69 (46) 26/69 (38)	 9/67 (13) 35/67 (52) 23/67 (34)	 20/136 (15) 67/136 (49) 49/136 (36)
	Disease-related symptoms, n (%) Fatigue Constitutional symptoms Hyperviscosity	 42 (56) 19 (25) 9 (12)	 49 (65) 29 (39) 10 (13)	 91 (61) 48 (32) 19 (13)
	Cytopenia at baseline, n (%) Hb ≤ 11 g/dl Platelets ≤ 100,000/mm^3 Absolute neutrophils ≤ 1500/mm^3	 44 (59) 4 (5) 4 (5)	 50 (67) 7 (9) 1 (1)	 94 (63) 11 (7) 5 (3)
	Median Hb (range), g/dl	10.5 (6.9–15.5)	10.0 (6.6–16.1)	10.3 (6.6–16.1)

Title: Ibrutinib with rituximab in adults with WM (iNNOVATE) [5, 7, 30]				
Study identifier	NCT02165397, EUDRACT2013-005478-22, PCYC-1127-CA, iNNOVATE			
	Bone marrow infiltration Median cellularity (range), % Median intrabecular space (range), %	 80(25–100) 36 (2–95)	 80 (2–100) 40 (1–95)	 80 (2–100) 38 (1–95)
	Serum IgM Median (range), g/litre ≥ 70 g/litre, n (%) ≥ 50 g/litre, n (%)	 32.9 (6.2–77.6) 2 (3) 17 (23)	 31.8 (5.9–83.3) 4 (5) 15 (20)	 32.4 (5.9–83.3) 6 (4) 32 (21)
	Median ß$_2$ microglobulin (range), mg/litre	3.4 (1.4–27.9)	3.9 (1.5–11.6)	3.7 (1.4–27.9)
	Extramedullary disease, n (%) Adenopathy Splenomegaly	59 (79) 56 (75) 9 (12)	60 (80) 58 (77) 18 (24)	119 (79) 114 (76) 27 (18)
	Previous systemic therapies, n (%) 0 1 or 2 ≥ 3	 34 (45) 34 (45) 7 (9)	 34 (45) 36 (48) 5 (7)	 68 (45) 70 (47) 12 (8)
	Previous rituximab-containing regimen, n/N (%)	36/41 (88)	34/41 (83)	70/82 (85)
Applicability of evidence				
Population	iNNOVATE was conducted in treatment-naïve WM patients and those with rituximab-sensitive disease recurrence with good performance-status (ECOG ≤ 2). The applicability of these results for patients with higher ECOG performance-status, cardiac risk factors, hypertension, bleeding or rituximab resistance needs further evaluation.			
Intervention	The dosage and administration of ibrutinib and rituximab used in iNNOVATE is consistent with that recommended for the treatment of WM [4]. Dose reduction or interruptions were allowed for any potentially study drug-related event and discontinued if toxicities persist.			
Comparators	Rituximab is indicated for symptomatic untreated WM. However, bendamustine and rituximab may also be appropriate as first-line therapy, bortezomib-rituximab-dexamethasone for symptomatic hyperviscosity, and ofatumumab in previously-treated WM intolerant to rituximab. Without direct comparison trials, physicians and patients may need to discuss whether adding ibrutinib to rituximab therapy would provide greater individualised efficacy than ibrutinib monotherapy.			
Outcomes	Follow-up is insufficient to evaluate OS and long-term safety. Mature OS data and QoL measures are needed to ensure patients achieve a clinically relevant benefit over time despite manageable toxicity.			
Setting	iNNOVATE is a multinational, study conducted in 45 sites across Australia, Canada, France, Germany, Greece, Italy, Spain, United Kingdom, and the United States.			

Abbreviations: BICR = blinded independent central review; BTK = Bruton tyrosine kinase; CI = confidence interval; CNS = central nervous system; CR = complete response; CRR = clinical response rate; CVD = cardiovascular disease; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FACT-An = Functional Assessment of Cancer Therapy-Anaemia; Hb = haemoglobin; HR = hazard ratio; IgM = immunoglobulin M; IPSSWM = International Prognostic Scoring System for Waldenström's Macroglobulinemia; IV = intravenous; IWWM = International Workshop on Waldenström's Macroglobulinemia; MR = minor response; MRU = medical resource utilization; NCCN = National Comprehensive Cancer Network; NR = not reported; ORR = overall response rate; PFS = progression-free survival; PR = partial response; QoL = quality of life; RCT = randomised controlled trial; TTNT = time to next treatment; WM = Waldenström's Macroglobulinemia; WT = wild type

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [32]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomised 1:1 to ibrutinib + rituximab or placebo + rituximab using the IWRS system. Randomisation was stratified according to the WM IPSS score assessed at screening (low versus intermediate versus high), prior systemic treatment regimens (0 versus 1-2 versus >3), and ECOG performance status score (0 or 1 versus 2).		yes
Adequate allocation concealment: centralised randomisation and allocation; blinded study medication was administered based on assignment from the IWRS		yes
Blinding:	**Patient:** centralised randomisation and allocation; received ibrutinib or matching placebo on an outpatient basis	yes
	Treating physician: centralised randomisation and allocation; patients received ibrutinib or matching placebo on an outpatient basis	yes
	Outcome assessor: centralised randomisation and allocation; BICR-assessed efficacy and safety at pre-specified interim analysis; sensitivity analysis was planned to assess PFS and ORR by predefined subgroups. Response defined based on modified Consensus Response Criteria from VIth International Workshop for WM, NCCN.	yes
Selective outcome reporting unlikely: primary endpoint of PFS, secondary endpoints of OS, ORR, Hb, TTNT, and AEs, and exploratory endpoints of investigator assessed PFS and ORR, DOR, CRR were reported. Other endpoints not included in this analysis are QoL and medical resource utilization, as per protocol.		yes
No other aspects which increase the risk of bias: industry funded the study, collected data, confirmed data for accuracy, compiled the data for analysis, performed statistical analysis, drafted and reviewed the manuscript.		no
Risk of bias – study level		low-risk

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPSSWM = International Prognostic Scoring System for Waldenström's Macroglobulinemia; IVRS/IWRS = interactive web response system; NCCN = National Cancer Care Network, WM = Waldenström's macroglobulinemia