Idelalisib (Zydelig®) in addition to rituximab for the treatment of relapsed chronic lymphocytic leukaemia

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 49
ISSN online 2076-5940

Idelalisib (Zydelig®) in addition to rituximab for the treatment of relapsed chronic lymphocytic leukaemia

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, November 2014

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft in collaboration with the Italian Horizon Scanning Project, Dipartimento Farmaceutico, Azienda ULSS 20, Verona/Italy (IHSP)

Authors: Dr. med. Eleen Rothschedl
Dr. Roberta Joppi (IHSP)
Dr. Chiara Poggiani (IHSP)
Internal review: Dr. med. Anna Nachtnebel, MSc
External review: Prof. Dr. med. Stephan Stilgenbauer
Klinik für Innere Medizin III
Hämatologie, Onkologie, Rheumatologie und Infektionskrankheiten, Universitätsklinikum Ulm

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

This product of collaboration with the Italian Horizon Scanning Project (IHSP) is an offspring of the European network for Health Technology Assessment (EUnetHTA) Project that was supported by a grant from the European Commission. The sole responsibility lies with the author(s), and the Commission is not responsible for any use that may be made of the information contained therein.

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicise the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at.

DSD: Horizon Scanning in Oncology No.49
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

© 2014 LBI-HTA – All rights reserved

1 Drug description

Generic/Brand name/ATC code:

Idelalisib/Zydelig®/L01XX47

Developer/Company:

Gilead Sciences, Inc.

Description:

Idelalisib (Zydelig®, GS-1101, CAL-101) is an inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3Kδ) which is expressed in normal and malignant B cells. By integrating and transmitting signals from surface molecules (e.g. B-cell receptor, cytokine and chemokine receptors, integrin β1) PI3Kδ regulates key cellular functions including growth, survival and migration. Idelalisib inhibits several cell-signalling pathways and thus proliferation and survival, and promotes apoptosis in many B-cell malignancies [1, 2].

idelalisib targets the B-cell receptor signalling pathway

Zydelig® is administered orally, twice daily, at a dosage of 150 mg; the treatment should be continued until disease progression (PD) or unacceptable toxicity occurs [3].

oral administration

2 Indication

Idelalisib (Zydelig®) is indicated in combination with rituximab in adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first-line treatment for patients with deletion 17p and/or TP53 mutation who are inappropriate candidates for chemoimmunotherapy [3].

idelalisib + rituximab are indicated in pretreated patients with CLL

3 Current regulatory status

After receiving a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in July 2014 [4], the EMA granted marketing authorisation for Zydelig® on 18 September 2014 for the following indications:

approved by the EMA since September 2014

- in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy,
- as monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment [3].

On 23 July 2014, the FDA approved Zydelig® for three types of blood cancer:

FDA approval in July 2014

- for relapsed CLL in combination with rituximab (in patients unsuitable for rituximab monotherapy due to other co-morbidities),

- for relapsed follicular B-cell non-Hodgkin lymphoma (in patients who have received at least two prior systemic therapies),
- for relapsed small lymphocytic lymphoma (in patients who have received at least two prior systemic therapies).

The FDA also granted orphan product designation for Zydelig® [5].

The Zydelig® prescribing information contains a boxed warning concerning potentially occurring fatal and serious toxicities (hepatotoxicity, severe diarrhoea, colitis, pneumonitis and intestinal perforation [2].

4 Burden of disease

CLL is mostly revealed by routine blood counts

CLL is a B-cell chronic lymphoproliferative disorder causing a progressive accumulation of functionally incompetent lymphocytes; it is the most common leukaemia in adults in Western countries. The incidence is 4.2/100.000 per year and increases to > 30/100.000 per year at an age over 80 years [6]. The median age at diagnosis is 72 years; older patients often cannot tolerate aggressive therapy regimens due to comorbidities and declining organ function [8].

Risk factors for CLL are a family history of CLL or other lymph-related cancers, older age, gender (men are more often affected than women) [7], ethnicity (CLL is more common in North America and Europe than in Asia) and certain chemical exposures [8].

The majority of CLL cases are diagnosed by routine blood counts showing lymphocytosis in otherwise asymptomatic patients. Signs discernible during physical examination indicating CLL may include lymphadenopathy, splenomegaly, hepatomegaly or skin lesions [9]. If existing, symptoms range from painless swelling of lymph nodes to symptoms corresponding to acquired immunodeficiency disorders such as infections or autoimmune complications. Only 5–10% of affected patients show the "typical" lymphoma symptoms (generally termed "B symptoms"):

- unintentional weight loss ≥ 10% of body weight within the previous 6 months,
- fevers of > 38°C for ≥ 2 weeks without evidence of infection,
- night sweats without evidence of infection,
- extreme fatigue.

median age at diagnosis: 72 years

Based on the results of physical examination and complete blood count, two staging systems are applied:

- the (modified) Rai staging system, assigning patients to a low risk (lymphocytosis), intermediate risk (lymphadenopathy, organomegaly) or high risk (anaemia, thrombocytopenia) group.
- the Binet staging system, consisting of stage A (< than 3 involved lymphoid sites), stage B (≥ 3 involved lymphoid sites) and stage C (presence of anaemia and/or thrombocytopenia) [9].

prognostic factors not decisive for treatment start

CLL prognosis is influenced by the presence of certain serum markers (thymidin-kinase, beta-2 microglobulin), genetic markers (including IGHV mutational status), cytogenetic abnormalities (deletion of 11q, 13q and 17p, CD38 expression and ZAP-70 expression) and other genetic lesions (including mutations in NOTCH1, SF3B1 and/or BIRK3 genes) [10]. There is evidence that some of those factors (17p deletion, 11q deletion, TP53, NOTCH1 and SF3B1 mutations) may play a role in chemorefractoriness and worse prognosis [11]. The presence of those prognostic factors should not be decisive for initiating CLL treatment [10]. However, presence of deletion 17p is guiding therapy and should be determined before initiation of any line of therapy. Likewise, testing for TP53 mutation should be performed before starting treatment. Data from the CLL8 trial suggests NOTCH1 mutation as a predictive factor for reduced benefit from adding rituximab to chemotherapy and SF3B1 mutation as a strong prognostic marker providing information on progression. Both findings need to be confirmed by additional clinical trials [12].

asymptomatic patients: observation

For asymptomatic patients, there is no need to start with CLL treatment immediately after diagnosis, but observation is the standard of care for those patients. Therapy is indicated if the following disease-related complications ("active disease") occur:

initiation of treatment when disease-related complications occur

- "typical" lymphoma symptoms,
- Rai stages III or IV, Binet stage C,
- autoimmune haemolytic anaemia and/or thrombocytopenia poorly responsive to corticosteroid therapy.
- Progressive disease (= increasing lymphocytosis with a lymphocyte doubling time less than 6 months and/or rapidly enlarging lymph nodes, spleen and liver) [13].

5 Current treatment

treatment options for relapsed CLL

Various treatment options exist for CLL patients depending on patient characteristics such as age or comorbidities and tumour characteristics. Depending on the patient's response to first-line therapy, relapsed or refractory disease can be differentiated. Relapsed disease is defined as a progressive disease after a period of six months or more after either a complete or partial remission had been achieved [14]. If patients do not respond to therapy, i.e. if they fail to achieve either a partial or complete remission with therapy, or if they develop a disease progression within six months of therapy, they have refractory disease [15].

After first-line therapy, further treatment will depend on the regimen administered previously, duration of remission, age and comorbidities. The following therapy options exist [1]:

- Second and subsequent line chemotherapy:
    - Combination therapy with fludarabine, cyclophosphamide and rituximab (FCR) if patients can tolerate it or if they responded well (PFS > 24 months) to first-line FCR [16] or bendamustine and rituximab (well-established, but few RCTs).

- For older patients or those with comorbidities who are not considered well enough for intensive cytotoxic chemotherapy (e.g. FCR), there is no recognised standard treatment. Options include chlorambucil with rituximab (in patients previously untreated with chemotherapy), bendamustine (with or without rituximab) or dose-reduced FCR.

- Biological therapy:
  - Rituximab may be used in combination with chemotherapy agents.
  - Other anti-CD20 monoclonal antibodies, such as ofatumumab, may be considered; ofatumumab is currently being used predominantly in patients who are refractory to rituximab and alemtuzumab.
  - Ibrutinib for CLL patients with 17p deletion which is associated with poor responses to standard treatment of CLL (approved by the FDA for this indication in July 2014)[5].
  - Allogeneic stem-cell transplantation should be considered for fit patients with high-risk CLL and should ideally be performed in the setting of a remission.
  - Alemtuzumab and methylprednisolone for patients with high-risk disease (with early relapse or TP53 deletion/mutation) when tolerated, or alemtuzumab with or without corticosteroids as an option for fitter patients who have failed other conventional therapies. However, the drug was voluntarily withdrawn by the marketing authorisation holder in Europe in 2012 [17].
- Radiotherapy: rarely used, may be indicated for patients with enlarged lymph nodes/spleen or prior to bone marrow transplant [1].

6 Evidence

384 references were identified by systematic literature search in 4 databases

A literature search was conducted in October 2014 in four databases (Medline, Embase, CRD Database and The Cochrane Library). Search terms were “Idelalisib”, “CAL 101”, “GS 1101” “Chronic lymphocytic leukaemia”, “Zydelig”. Also, the manufacturer was contacted for any further evidence, and submitted 2 references (one of them already identified by the systematic literature search) and general information about current idelalisib trials.

Overall, 384 references were identified; one phase III trial [18] was included in this report.

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia [18, 19]			
Study identifier	NCT01539512, EudraCT Number 2011-005180-24, Trial protocol ID GS-US-312-0116		
Design	Multicentre, randomised, double-blind, placebo-controlled		
	Duration	*Enrolment:* May 2012–August 2013 *Median follow-up:* NR *Data cut-off dates for analyses:* 2013-08-30 (first interim analysis), 2013-10-09 (second interim analysis)	
Hypothesis	Superiority The sample size provided a power of more than 85% to detect a 75% improvement in the median PFS. Two interim analyses were pre-specified after approximately 50% and 75% of the anticipated 119 events had occurred, at alpha levels of 0.001 and 0.005, respectively.		
Funding	Gilead Sciences, Inc.		
Treatment groups	Intervention (n=110)	Idelalisib 150 mg (oral) twice daily + rituximab intravenously at a dose of 375 mg per square metre of body-surface area, followed by 500 mg per square metre every 2 weeks for 4 doses and then every 4 weeks for 3 doses (for a total of 8 infusions)	
	Control (n=110)	Placebo (oral) twice daily + rituximab intravenously at a dose of 375 mg per square metre of body-surface area, followed by 500 mg per square metre every 2 weeks for 4 doses and then every 4 weeks for 3 doses (for a total of 8 infusions)	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Interval from randomisation to disease progression or death from any cause
	Overall survival	OS	Interval from randomisation to death from any cause
	Rate of overall response	ORR	Proportion of patients who had a complete or partial response on the basis of the IWCLL modified criteria
	Lymph-node response rate	-	Proportion of patients who had a decrease of 50% or more in lymphadenopathy
Results and analysis			
Analysis description	Intention-to-treat analysis PFS calculated by using the Kaplan-Meier method, rates compared by using a stratified log-rank test Hazard ratios calculated by using a Cox model with adjustment for stratification For binary-response end points the Cochran-Mantel-Haenszel chi-square test, adjusted for stratification, was used		
Analysis population	Inclusion	❖ CLL that had progressed within 24 months after the last treatment ❖ Patients unable to receive cytotoxic agents for one or more of the following reasons: - Severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies - An estimated creatinine clearance of less than 60 ml per minute - A score on the CIRS of more than 6 for coexisting illnesses not related to CLL	

		✿ Previous treatment must have included either a CD20 antibody-based regimen or at least two previous cytotoxic regimens		
	Exclusion	✿ Known histological transformation from CLL to an aggressive lymphoma ✿ Presence of intermediate- or high-grade myelodysplastic syndrome		
	Characteristics		Intervention	Control
		Gender, male, %	69	62
		Median age (range), years	71 (48–90)	71 (47–92)
		Rai stage, % of patients 0 1 or 2 3 or 4 Missing data	 0 31 64 5	 1 26 65 7
		Extent of CLL, % of patients Anaemia: any grade/grade ≥3 Neutropenia: any grade/grade ≥3 Thrombocytopenia: any grade/ grade ≥3	 75/6 34/17 62/16	 72/11 35/16 61/29
		Median absolute lymphocyte count, per mm^3	31,960	30,880
		Median estimated creatinine clearance, ml/min	62	67
		Genetic stratification factors, % of patients Unmutated IGHV 17p deletion or TP53 mutation	 83 42	 85 45
		Median CIRS score	8	8
		Previous CLL treatment - median number of drugs (range) - Drugs, % of patients o Rituximab o Cyclophosphamide o Fludarabine o Bendamustine o Chlorambucil	 3 (1–12) 91 64 56 58 31	 3 (1–9) 88 70 64 54 22

Descriptive statistics and estimated variability	Treatment group	*Idelalisib + rituximab*	*Placebo + rituximab*
	Number of subjects	N=110	N=110
	Median PFS, months	NR	5.5
	PFS at 24 weeks, %	93	46
	Median OS, months	NR	NR
	OS at 12 months, %	92	80
	ORR, %	81	13
	Lymph node response, reduction rate, %	93	4
Effect estimate per comparison	*Comparison groups*		*Intervention vs. Control*
	PFS (August 2013)	HR	0.15
		95% CI	0.08–0.28
		P value	<0.001

	PFS (October 2013) [19]	HR	0.18
		95% CI	0.10–0.32
		P value	<0.001
	OS (August 2013)	HR	0.28
		95% CI	0.09–0.86
		P value	0.02
	OS (October 2013)	HR	0.28
		95% CI	0.11–0.69
		P value	0.003
	ORR	Odds ratio	29.92
		95% CI	NA
		P value	<0.001
	Lymph node response	Odds ratio	264
		Variability	-
		P value	<0.001

Abbreviations: CI = confidence interval, CIRS = Cumulative Illness Rating Scale (ranges from 0 to 56, with higher scores indicating an increased number or greater severity of coexisting illness), CLL = chronic lymphocytic leukaemia, IWCLL = International Workshop on Chronic Lymphocytic Leukaemia, NA = not available, NR = not reached, Rai = system for staging CLL (0=low-risk disease, 1–2=intermediate risk, 3–4=high risk), ORR = overall response rate, OS = overall survival, PFS = progression-free survival

Table 2: Most frequent adverse events

NCT01539512				
Adverse Event (according to NCI-CTCAE version 4.03)	**Idelalisib + rituximab (N=110)**		**Placebo + rituximab (N=107)**	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
AEs during treatment	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (21)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhoea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (15)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Constipation	13 (12)	0	12 (11)	0
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Vomiting	13 (12)	0	8 (7)	0
Dyspnoea	12 (11)	2 (2)	20 (19)	3 (3)
Night sweats	11 (10)	0	8 (7)	0
Rash	11 (10)	2 (2)	6 (6)	0
Serious AEs	44 (40)	NA	37 (35)	NA
Discontinuation due to AEs, %	9 (8)		11 (10)	

Abbreviations: AE = adverse event, NCI = National Cancer Institute, CTCAE = Common Terminology Criteria for Adverse Events, NA = not applicable (serious adverse events are reported as severe regardless of the severity grading)

a phase III trial compared efficacy and safety of idelalisib + rituximab to placebo + rituximab in 220 patients

This multicentre, randomised, double-blind, placebo-controlled phase III study [18] evaluated the efficacy and safety of idelalisib combined with rituximab compared to placebo plus rituximab. A total of 220 CLL patients were included, all of whom had progressed within 24 months after the last therapy. Prior administered treatment must have included at least two previous cytotoxic regimens or a CD20 antibody-based regimen. The median number of prior drugs was 3; applied regimens were rituximab, cyclophosphamide, fludarabine, bendamustine and chlorambucil. All patients were ineligible for cytotoxic therapy due to different reasons: severe neutropenia or thrombocytopenia, an estimated creatinine clearance of less than 60 ml per minute or a CIRS score of more than 6. The median age of patients in both groups was 71 years, 64% (idelalisib group) and 65% (placebo group) of patients were assigned to Rai stage 3 or 4. Median CIRS score was 8 in both groups. 83% (idelalisib group) and 85% of patients (placebo group) had an unmutated IGHV status, and 42% (idelalisib group) and 45% (placebo group) of patients showed 17p deletion or TP53 mutation.

At the beginning of study treatment, all patients received rituximab intravenously. After stratification according to genetic factors (unmutated IGHV, 17p deletion or TP53 mutation), the patients were randomly assigned to two treatment arms: the idelalisib group (receiving idelalisib at a dosage of 150 mg twice daily plus rituximab) and the placebo group (receiving placebo plus rituximab). The median duration of treatment was 3.8 months in the idelalisib group versus 2.9 months in the placebo group.

The primary end point of the study was PFS; secondary endpoints were the rates of overall and complete response, lymph node response and overall survival. Furthermore, the idelalisib-associated lymphocytosis was a measured value.

median PFS was 5.5 months in the placebo group and was not reached by the idelalisib group

After 24 weeks of treatment, the rate of PFS was 93% in the idelalisib group compared to 46% in the placebo group. The median PFS was 5.5 months in the placebo group and was not reached by the idelalisib group (HR 0.15, 95% CI 0.08–0.28, $p<0.001$). After the second interim analysis in October 2013, the results remained the same [19]. The positive effect of idelalisib and rituximab was observed in all pre-specified subgroups as well, regardless of the presence or absence of genetic factors.

improved rates of OS and overall response in the idelalisib group

The OS rate at 12 months was 92% in the idelalisib group versus 80% in the placebo group, with an adjusted HR for death of 0.28 (95% CI 0.09–0.86, $p=0.02$); 4% (idelalisib group) and 11% (placebo group) of study patients died while participating. The ORR (all partial responses) was 81% in the idelalisib group compared to 13% in the placebo group. Analysis of post-baseline conducted imaging procedures showed a significant higher reduction of 50% or more in lymphadenopathy in the idelalisib group than in the placebo group.

Lymphocyte count showed a peak at week 2 and resolved by week 12 in the idelalisib group, while starting to increase at week 24 (after rituximab administration ended) in the placebo group.

In the highest-risk patients, who were positive for both 17p deletion and TP53 mutation, the combination therapy achieved 76.5% ORR and PFS HR 0.13 [20].

At least one adverse event (AE) occurred in 90% of patients in each treatment group, but most of them were grade 2 or lower. The most common AEs in the idelalisib group were pyrexia, fatigue, nausea, chills and diarrhoea; in the placebo group infusion-related reactions, fatigue, cough, nausea and dyspnoea were most frequent. 40% (idelalisib group) and 35% (placebo group) of patients had at least one serious AE: pneumonia, pyrexia and febrile neutropenia were most common. Laboratory abnormalities more frequent in the idelalisib group compared to the placebo group were ALT (alanine aminotransferase) or AST (aspartate aminotransferase) elevation (35% vs. 19%) and neutropenia (55% vs. 49%).

serious adverse events occurred in 40% (idelalisib group) and 35% (placebo group)

8% of patients in the idelalisib group and 10% of patients in the placebo group discontinued study treatment due to AEs. Most commonly, disease progression was causal for discontinuing study treatment.

The statistically significant improvement in the rate of PFS was the deciding factor to terminate the study after the first pre-specified interim analysis. Patients who had disease progression during placebo treatment could receive idelalisib in an extension study (NCT01539291, estimated study completion date is December 2015). For patients who had disease progression despite receiving idelalisib, the administration of an increased dose (300 mg twice a day) was provided.

study has been terminated after the first interim analysis due to significant improved PFS

Additionally, health-related quality-of-life (HRQL) was evaluated among the two treatment arms. The 44-item Functional Assessment of Cancer Therapy-Leukemia scale (FACT-Leu) was used for this purpose, measuring physical, functional, social and emotional well-being as well as leukaemia-specific concerns. [21]. Compared to the control arm, idelalisib-receiving patients showed statistically significant and clinically meaningful improvements in HRQL FACT-Leu measurements [19]. These results were only published in an abstract.

6.2 Efficacy and safety – further studies

No phase II studies that fit the purpose of this assessment were identified.

7 Estimated costs

One package Zydelig® containing 60 tablets at 150 mg costs € 4,395.50 [22]. Assuming that two 500 mg MabThera® infusions are needed for each rituximab infusion, costs for the regimen used in the study (150 mg idelalisib twice daily + 8 infusions rituximab) would amount to about € 47,190 for 5 months or to € 9,440 per month. Continuation of Zydelig® therapy and the treatment of side effects are not included.

idelalisib costs € 4,395 in Austria

8 Ongoing research

In October 2014, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following trials were identified:

4 ongoing phase III trials identified

- NCT01539291 (EudraCT number: 2011-006293-72): a multicentre, 2-arm, double-blind, parallel-group extension study (phase III) aims to evaluate the effect of idelalisib on the onset, magnitude and duration of tumour control. It is a companion study for patients with CLL who participated in study GS-US-312-0116. Estimated study completion date is December 2015.
- NCT02136511 (EudraCT number: 2013-005343-82): an expanded access study (idelalisib in combination with rituximab) for previously treated patients with relapsed CLL.

Ongoing phase III trials evaluating idelalisib combination therapies:

- NCT01569295 (EudraCT number: 2011-006292-20): a phase III, randomised, double-blind, placebo-controlled study assessing the effect of idelalisib in combination with bendamustine and rituximab for previously treated CLL. Estimated study completion date is December 2017.
- NCT01659021 (EudraCT number: 2012-001236-65): this randomised, controlled phase III study evaluates the efficacy and safety of idelalisib in combination with ofatumumab in previously treated patients with CLL. Estimated study completion date is November 2016.

There are several phase I and phase II studies ongoing, assessing the effect of idelalisib on relapsed CLL as a single agent or in combination with other drugs. Furthermore, different trials evaluate the efficacy of idelalisib on other types of cancer, including SLL, indolent non-Hodgkin lymphomas, follicular lymphomas or multiple myeloma.

9 Commentary

approved by both the EMA and the FDA

Idelalisib (Zydelig®) affects CLL cell functions by targeting the B-cell receptor signalling pathway. It has been approved by the EMA in September 2014; the FDA granted marketing authorisation in July 2014. Idelalisib is indicated in adult patients with CLL who have received at least one prior therapy and as first-line regimen for patients with 17p deletion or TP53 mutation status who are unsuitable for chemoimmunotherapy [2, 3].

These decisions were based on a phase III trial assessing idelalisib with rituximab in comparison to placebo with rituximab in 220 patients. All patients had been previously treated and were considered ineligible for (further) cytotoxic therapy [18].

The median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group. At 24 weeks, the PFS rate was 93% in the idelalisib group compared to 46% in the placebo group. The OS rate was 92% (idelalisib group) versus 80% (placebo group) at 12 months; median duration of OS also was not reached in either of the two treatment arms. ORR was 81% in the idelalisib group compared to 13% in the placebo group. The proportion of patients who had lymphadenopathy reduction of 50% or more was significantly higher in the idelalisib group than in the placebo group.

PFS, ORR and OS were significantly improved in idelalisib group

An important finding of this trial was the treatment effect of idelalisib plus rituximab combination therapy on the pre-specified subgroups: the results in patients with genetic factors including 17p deletion, TP53 mutation or unmutated IGHV were superior to rituximab monotherapy [18]. As patients with these genetic lesions have a very poor outcome anyway and no uniform regimen for their optimal therapy exists, targeting the B-cell receptor signalling pathway may yield better outcomes [23].

The idelalisib-associated lymphocytosis showed a peak at weeks 2 and vanished at week 12 in the idelalisib group while starting to increase at week 24 in the placebo group [18]. Appointed as a single agent, idelalisib mobilises malignant cells from tissues into peripheral blood where they may be more responsive to combination therapy [24].The mechanism of malignant B-cell release leads to a period of transient lymphocytosis that can be shortened by the addition of rituximab [25]. When lymphocytosis occurs during idelalisib treatment and there is no other evidence on disease progression (PD), the therapy should be continued until other definitive symptoms of PD appear [26].

At least one AE occurred in 90% of patients in each group, but most of them were grade 2 or lower. Most common AEs were pyrexia, fatigue, nausea, chills and diarrhoea in the idelalisib group, and infusion-related reactions, fatigue, cough, nausea and dyspnoea in the placebo group. 40% of patients in the idelalisib group and 35% of placebo group patients had at least one serious AE; most frequently were pneumonia, pyrexia and febrile neutropenia. Nonetheless, only 8% of patients in the idelalisib group and 10% of patients in the placebo group discontinued study treatment due to AEs.

serious adverse events in 40% (idelalisib group) and 35% (placebo group) of patients

The trial was stopped early as a result of meeting its efficacy endpoints at the first interim data analysis. Patients from the placebo group were then offered therapy with idelalisib [27, 28]. The early termination of the study caused a lack of data in long-term efficacy (median duration of exposure was about 5 months). Thus, further follow-up of the study population is required, especially because long treatment duration is expected in clinical practice [19]. In terms of safety, the potential occurrence of late side effects needs to be evaluated [29]. The idelalisib extension study (NCT01539291) may provide further information in this regard.

phase III trial met efficacy points and was stopped early

long-term data on safety and efficacy are required

For patients with relapsed CLL who are not eligible for intensive cytotoxic therapy (due to older age or comorbidities), chlorambucil (+/- rituximab), bendamustine (+/- rituximab) or dose-reduced FCR provide options [1]. Therefore the question is whether rituximab in addition to placebo is a suitable comparator, especially since rituximab alone is not licensed in Europe for the treatment of CLL. Despite this, rituximab-only treatment is an option frequently used in clinical practice for patients truly ineligible for chemotherapy. It remains unknown whether the included patients were indeed ineligible for further chemotherapy as a proper definition for these patients is not available [19]. However, the criteria applied for including

positive treatment effects also among "high risk" patients

chemotherapy-ineligible patients in the phase III trial, i.e. severe myelosuppression from previous chemotherapy, reduced kidney function, or a CIRS score of more than 6 for non-CLL-related coexisting illnesses, are based on the suggestion of the German Leukaemia Study Group.

a variety of comparators exist; ibrutinib has been approved for the same indication recently

Over the past few years, a number of novel agents were evaluated for the treatment of CLL, including ibrutinib, ofatumumab or alemtuzumab, as combination regimens or as single agents. Idelalisib is already the second kinase inhibitor specifically targeting CLL cells; recently, ibrutinib (Imbruvica®) has been approved by the EMA and the FDA for the treatment of patients with CLL who have received at least one prior therapy or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy. The approval decision was based on the results of the RESONATE trial, comparing ibrutinib versus ofatumumab in 391 pretreated CLL patients. In this study, patients were at a median age of 67 years and 32% of them had a CIRS score of more than 6 [30]. In the idelalisib trial, patients had a median age of 71 years and 85% of them had a CIRS score of more than 6 and may thus be more representative of the potential target group. However, the direct comparison of idelalisib with ibrutinib may yield information as to which drug the patients benefit from the most. Further drugs in development are alvocidib, dinaciclib and duvelisib, all targeting CLL cell survival pathways [6].

costs for ibrutinib therapy higher than for idelalisib monotherapy but less expensive than for idelalisib in combination with rituximab

Both idelalisib and ibrutinib were granted marketing authorisation by the EMA and the FDA. One package ibrutinib containing 90 tablets at 140 mg costs € 6,598 which correspond to the monthly treatment costs assuming the administration of the recommended dose of 420 mg once daily [22]. Thus, the price for idelalisib is currently lower than for (single-agent) ibrutinib. However, for idelalisib in combination with rituximab (or other cancer treatments), costs exceed those for ibrutinib single-agent therapy. Additionally, in contrast to ibrutinib, idelalisib contains a boxed warning on side effects such as colitis, lung inflammation and potential fatal liver problems, which may influence the drug's success on the market [31]. An aspect that needs resolving with regard to both drugs is the development of resistance. There is evidence that intervening in the PI3K pathway could lead to drug resistance by up-regulation or activation of other PI3K isoforms [32].

for both agents: potential development of resistance?

optimal treatment needs to be chosen individually

Opinions concerning incorporating idelalisib in the complex treatment of CLL are currently diverging: on the one hand, the majority of CLL patients may potentially be spared toxic chemotherapy, on the other hand, chemotherapy combined with targeted therapies may be practicable in patients diagnosed in middle age or younger [27]. Choosing the appropriate therapy for elderly patients with CLL is an individual decision, considering the stage of the disease and risk factors as well as the patient's physical condition and drug tolerability [33]. Possibly, the final results of the HRQL measurements (information currently only available as abstract publication) will contribute to guiding treatment decisions.

The introduction of novel agents has influenced the management of high-risk CLL, challenging the indication and timing of allogeneic haematopoietic stem cell transplantation (HSCT). For fit patients with high-risk CLL, HSCT has been considered as the treatment of choice, representing the only modality with documented curative potential in CLL. In contrast, both treatment-related mortality and morbidity are likely to be significantly lower with BCR-signal inhibitors/BCL2 antagonists as compared with HSCT (although more information is needed at that point). However, there is no

long-term data available on the efficacy of these novel agents. Hence, the HSCT option should be included in a treatment decision process [34].

In conclusion, combination therapy of idelalisib and rituximab offers a new treatment option for patients with relapsed CLL who are ineligible for cytotoxic therapy; particularly for those with genetic factors including 17p deletion, TP53 mutation or unmutated IGHV. Nevertheless, further trials are needed to evaluate efficacy and safety in the long-term use of idelalisib, as well as the important issue of potential idelalisib resistance.

feasible treatment option for patients with relapsed CLL who are ineligible for cytotoxic therapy

References

[1] National Institute for Health Research – Horizon Scanning Centre. Idelalisib with rituximab for chronic lymphocytic leukaemia. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC) 2013.

[2] U.S. Food and Drug Administration. Drugs@FDA. 2014 [cited 2014-10-28; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf

[3] EMA. Zydelig. Product information. 2014 [cited 2014-10-28; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf

[4] Committee for Medicinal Products for Human Use (CHMP). Zydelig. Summary of opinion. 2014 [cited 2014-10-29; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003843/WC500170181.pdf

[5] U.S. Food and Drug Administration. FDA News Release. 2014 [cited 2014-11-07; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406387.htm

[6] Italian Horizon Scanning Project. New Product Information Report. Idelalisib. 2014.

[7] Cancer.Net. CLL: Risk Factors. 2014 [cited 2014-10-28; Available from: http://www.cancer.net/cancer-types/leukemia-chronic-lymphocytic-cll/risk-factors

[8] Society AC. Chronic Lymphocytic Leukemia. Risk Factors. 2014 [cited 2014-10-28; Available from: http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-risk-factors

[9] UpToDate. Staging and prognosis of chronic lymphocytic leukemia. 2014 [cited 2014-10-28; Available from: http://www.uptodate.com/contents/staging-and-prognosis-of-chronic-lymphocytic-leukemia?source=see_link

[10] National Comprehensive Cancer Network. NCCN Guidelines. Non-Hodkin´s Lymphomas. Version 4.2014. 2014 [cited 2014-10-30; Available from: www.nccn.org

[11] Cuneo A, Cavazzini F, Ciccone M, Daghia G, Sofritti O, Saccenti E, et al. Modern treatment in chronic lymphocytic leukemia: Impact on survival and efficacy in high-risk subgroups. Cancer Medicine. 2014;3(3):555-64.

[12] Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Döhner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123(21).

[13] UpToDate. Overview of the treatment of chronic lymphocytic leukemia. 2014 [cited 28-10-2014]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-chronic-lymphocytic-leukemia?source=search_result&search=cll&selectedTitle=2~150

[14] Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner 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 Jun 15;111(12):5446-56.

[15] Hallek M CB, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner 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 Jun 15 Jun 15;111(12):5446-56.

[16] Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2010;2010:481-8.

[17] European Medicines Agency. Public statement - MabCampath (alemtuzumab) Withdrawal of the marketing authorisation in the European Union 2012.

[18] Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2014 Mar 13;370(11):997-1007.
[19] CHMP assessment report 2014-07-24. Zydelig.Procedure No.: EMEA/H/C/003843/0000. 2014 [cited 2014-11-10; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003843/WC500175379.pdf
[20] Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Efficacy of idelalisib in CLL subpopulations harboring del(17p) and other adverse prognostic factors: Results from a phase 3, randomized, double-blind, placebo-controlled trial. Journal of Clinical Oncology. 2014;32(15).
[21] Ghia P, O'Brien SM, Hillmen P, Furman RR, Coutre SE, Sharman JP, et al. Health-related quality of life (HRQL) impact of idelalisib (IDELA) in patients (pts) with relapsed chronic lymphocytic leukemia (CLL): Phase 3 results. Journal of Clinical Oncology. 2014;32(15).
[22] Warenverzeichnis. 2014 [cited 18-12-2014]; Available from: warenverzeichnis.apoverlag.at
[23] Sellner L, Denzinger S, Dietrich S, Glimm H, Merkel O, Dreger P, et al. What do we do with chronic lymphocytic leukemia with 17p deletion? Current Hematologic Malignancy Reports. 2013;8(1):81-90.
[24] Brown JR, Jahn TM, Furman RR, Leonard JP, Spurgeon SE, Byrd JC, et al. Patterns of nodal response and lymphocytosis in patients with previously treated CLL receiving the selective phosphatidylinositol 3-kinase-delta (PI3K(delta)) inhibitor, cal-101 (GS-1101) alone or in combination with rituximab (R) or bendamustine (B). Clinical Lymphoma, Myeloma and Leukemia. 2011;11((Brown J.R.) Dana Farber Cancer Institute, Boston, United States):S272-S3.
[25] Fruman DA, Cantley LC. Idelalisib--a PI3K inhibitor for B-cell cancers. New England Journal of Medicine. 2014 Mar 13;370(11):1061-2.
[26] Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. Journal of Clinical Oncology. 2012;30(23):2820-2.
[27] Idelalisib, ibrutinib show benefits in CLL. Cancer Discovery. 2014 Apr;4(4):382.
[28] Gilbert JA. Idelalisib: targeting PI3K in B-cell malignancies. Lancet Oncology. 2014 Mar;15(3):e108.
[29] Foa R. Changes in the treatment landscape for chronic lymphoid leukemia. New England Journal of Medicine. 2014;371(3):273-4.
[30] Nachtnebel A., Breuer J. Ibrutinib (Imbruvica®) for relapsierte oder refraktäre chronisch lymphatische Leukämie. DSD: Horizon Scanning in Oncology 47. [cited 2014-11-10; Available from: http://eprints.hta.lbg.ac.at/1037/
[31] FiercePharma. UPDATED: Europe approves Gilead's cancer drug Zydelig amid challenging pricing environment. 2014 [cited 2014-11-10; Available from: http://www.fiercepharma.com/story/europe-approves-gileads-cancer-drug-zydelig-amid-challenging-pricing-enviro/2014-09-19
[32] Khan M, Saif A, Sandler S, Mirrakhimov AE. Idelalisib for the treatment of chronic lymphocytic leukemia. Isrn Oncology Print. 2014;2014:931858.
[33] Mozaheb Z. Treating the elderly patient with chronic lymphocytic leukemia: Current and emerging options. Blood and Lymphatic Cancer: Targets and Therapy. 2014;4((Mozaheb Z., mozahebz@mums.ac.ir) Department of Hematology-Oncology, Imam-Reza Hospital, Mashhad University of Medical Science, Mashhad, Iran):9-14.
[34] Dreger P, Schetelig J, Andersen N, Corradini P, van Gelder M, Gribben J, et al. Managing high-risk chronic lymphocytic leukemia during transition to a new treatment era: stem cell transplantation or novel agents? Blood.