Horizon Scanning in Oncology

Ibrutinib (Imbruvica®) for relapsed or refractory chronic lymphocytic leukaemia

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1 Drug description

Generic/Brand name/ATC code:

Ibrutinib/Imbruvica®/L01XE27

Developer/Company:

Distributed and marketed by Pharmacyclics Inc. and marketed by Janssen-Cilag International NV.

Description:

ibrutinib is a first-in-class inhibitor of Bruton's Tyrosine Kinase

Ibrutinib is a first-in-class, small-molecule inhibitor of Bruton's Tyrosine Kinase (BTK). It covalently binds to and therefore irreversibly inhibits BTK. Since BTK is a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways, the proliferation and survival, but also the migration and homing of malignant B-cells are inhibited [1].

420 mg orally once daily

The recommended dosage of ibrutinib for the treatment of chronic lymphocytic leukaemia (CLL) is 420 mg taken orally once daily (three 140 mg capsules once daily). Therapy should be continued until disease progression or unacceptable toxicities. Since bleedings, infections, renal failure and second primary malignancies have been reported, monitoring for occurrence of these adverse events is indicated throughout therapy [2].

2 Indication

ibrutinib for ≥second-line CLL therapy or first-line in patients with 17p deletion or TP53 mutation

Ibrutinib (Imbruvica®) for the treatment of patients with CLL who have received at least one prior therapy or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.

3 Current regulatory status

positive CHMP recommendation for CLL in July 2014

In Europe, Imbruvica® was designated as an orphan medicinal product on the 26th of April 2012 for the treatment of mantle cell lymphoma, and on the 12th March 2013 for the treatment of CLL. The Committee for Medicinal Products for Human Use (CHMP) formulated a positive recommendation on the 24th of July 2014 to grant market authorisation for ibrutinib for:

- The treatment of adult patients with CLL who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.
- The treatment of adult patients with relapsed or refractory mantle cell lymphoma [3, 4].

FDA licensing in July 2014 for CLL

In the U.S., the FDA licensed ibrutinib with priority review for patients with:

- CLL who have received at least one prior therapy in February 2014 or with 17p deletion in July 2014.
- mantle cell lymphoma who have received at least one prior therapy in November 2013 [2].

4 Burden of disease

CLL most common form of leukaemia in industrialised countries affecting mostly patients ≥ 65 years

CLL belongs to the group of indolent B-cell non-Hodgkin lymphomas (NHL) and is the most common type of adult leukaemia in Western countries, accounting for approximately 25% to 30% of all leukaemias [5]. The median age at diagnosis is 72 years [6]. Thus, 70% of patients are older than 65 years at diagnosis and CLL is rarely seen in younger persons, with fewer than 2% of patients being younger than 45 years at the time of diagnosis. The male to female ratio is 2:1 [5, 7].

risk factors: age, sex, ethnicity, family history, other cancers

Risk factors for developing CLL include older age, male sex, white ethnicity, family history of CLL or other blood and bone marrow cancers [8].

most patients are asymptomatic at diagnosis and are diagnosed incidentally

In the majority of cases, CLL is diagnosed incidentally by routine complete blood count examination, because most patients are asymptomatic at the time of diagnosis. Diagnosis is established by blood counts, blood smears and immunophenotyping of circulating B-lymphocytes [9]. The most common symptom is lymphadenopathy, followed by so-called "B" symptoms, including fever, night sweats and weight loss. The life expectancy of patients with early-stage disease at diagnosis is greater than ten years, but decreases with advanced disease at diagnosis [10, 11].

two classification systems for CLL: Rai classification, Binet staging system

There are two classification systems for the clinical staging of CLL, depending on standard laboratory tests and physical examination, including the Rai classification and the Binet staging system. The Rai classification distinguishes three stages:

- low (formerly Rai stage 0): lymphocytosis
- intermediate (formerly Rai stage I or II): lymphadenopathy, organomegaly
- high (formerly Rai stage IV and V) risk disease: anaemia, thrombocytopenia.

watch and wait in early stage of disease

therapy indicated when disease-specific symptoms, symptomatic/progressive anaemia and/or thrombocytopenia, progressive bulky disease or increasing lymphocytosis

The Binet staging is subdivided into stages A, B and C [12]. The initiation of treatment is not recommended for asymptomatic early-stage disease (Rai 0, Binet A). In these patients, a watch-and-wait strategy with checks of blood cell counts and clinical examination every six months is recommended until there is evidence of disease progression; if the disease is stable, yearly intervals are sufficient. In patients with intermediate and high-risk disease according to the Rai classification, as well as patients with Binet stage B or C disease, the initiation of treatment is recommended, whereas some patients with intermediate disease or Binet stage B may also be monitored until the disease progresses [13]. Therapy is indicated when disease-specific symptoms (i.e., severe fatigue, night sweats, weight loss, painful lymphadenopathy, or fever without infection), symptomatic/progressive anaemia and/or thrombocytopenia, progressive bulky disease (spleen > 6 cm below costal margin, lymph nodes > 10 cm) or increasing lymphocytosis with a lymphocyte doubling time of less than six months occur [14, 15].

In addition to these stages, prognosis depend on other factors such as serum markers thymidinekinase and beta-2 microglobulin, genetic markers including immunoglobulin heavy chain variable (IGHV) mutational status and cytogenetic abnormalities detected by fluorescence in situ hybridisation (e.g., del[13q], del[11q], del[17p]), CD38 expression, and ZAP-70 expression [14, 16].

80% of patients show cytogenetic abnormalities

Presence of unmutated IGHV, expression of CD38 (≥ 7% of B lymphocytes) and/or ZAP-70 are associated with a poor prognosis. Cytogenetic abnormalities are present in about 80% of previously untreated CLL patients. Del(11q) (in about 18%) also leads to shorter median survival and to disease progression. Del(17p) can be found in about 7% of all patients and is associated with the poorest prognosis. Together with del(17p), patients with a mutation of the p53gene (5–10% of the patients) have the poorest prognosis, resulting in a median overall survival of about 2–3 years [17]. In contrast, elevated levels of serum beta-2 microglobulin and del(13q) are predictors for a more favourable prognosis [14].

poor prognostic factors: unmutated IGHV, Del(17p), del(11q)

5 Current treatment

The choice of first-line therapy depends on co-morbidities (measured, for example, by the Cumulative Illness Rating Scale), genetic status and renal function.
If the disease has progressed on first-line therapy, further treatment will depend on the regimen administered previously, duration of remission, age and co-morbidities.
Depending on the response to first-line therapy, relapsed and refractory disease can be distinguished. Relapsed disease is defined as a progressive disease after a period of six months or more after either a complete or partial remission has been achieved [18]. If patients do not respond to therapy, i.e., 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.

treatment options depending on stage, age, cytogenetic lesions, other diseases

Treatment options for refractory/relapsed CLL include:

- 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 [19] or bendamustine and rituximab (well-established, but few RCTs).
  - For older patients or those with co-morbidities 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.
  - Idelalisib in combination with rituximab (positive CHMP decision was issued in July 2014).
- Biological therapy:
  - Rituximab may be used in combination with chemotherapy agents.

treatment options for CLL

- 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.
- 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 [20].

- Radiotherapy: rarely used, but may be indicated for patients with enlarged lymph nodes, an enlarged spleen or prior to bone marrow transplant [1].

6 Evidence

systematic search in four databases yielded 235 references

A systematic literature search was conducted in four databases (Ovid Medline, Embase, Cochrane Library, CRD Database) on the 22nd of July 2014. Search terms were Ibrutinib, pci-32765, pci 32765, pci32765, imbruvica and 'chronic lymphocytic leukemia', 'chronic lymphocytic leukemias', 'chronic lymphocytic leukaemia' or 'chronic lymphocytic leukaemia. The systematic search yielded 235 references overall, and the manufacturer submitted seven publications overall. Of these, all but two had already been identified by the systematic literature search, resulting in 237 references overall. Of all identified articles, two references were included: one phase III trial [21] and one phase II study [22].

6.1 Efficacy and safety – Phase III studies

Table 1: Summary of efficacy

Study title Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia [21, 23]		
Study identifier	Clinical Trials No: NCT01578707; PCYC-1112-CA, EudraCT No: 2012-000694-23; RESONATE	
Design	Multicentre (67 sites in the U.S., Europe and Australia), open-label, phase 3 study stratified according to whether they had resistance to purine analogue chemoimmunotherapy (defined as no response or a relapse within 12 months after the last dose of a purine analogue) and whether they had a chromosome 17p13.1 deletion	
	Duration	*Enrolment:* June 2012–April 2013 *Median follow-up:* 9.4 months (range 0.1 – 16.6) *Cut-off dates for analyses:* NA
Hypothesis	Superiority Number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%. Assuming median PFS for the ofatumumab arm is eight months as measured from the date the patient is randomised, a target	

	hazard ratio of 0.6 corresponds to a 66.7% increase in median PFS for the ibrutinib arm relative to the ofatumumab arm (increase from 8 months to 13.31 months).		
Funding	Pharmacyclics and Janssen		
Treatment groups	Overall study participants = 391		
	Intervention (n = 195)	oral ibrutinib (at a dose of 420 mg once daily) until disease progression or the occurrence of unacceptable toxic effects	
	Control (n = 196)	iv ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for seven weeks and then every four weeks for 16 weeks	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	assessed by independent review committee per International Workshop on Chronic Lymphocytic Leukaemia 2008 criteria [18]
	Overall survival	OS	time from date of randomisation until date of death due to any cause
	Response rate	ORR	defined as the proportion of patients who achieve complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR), or partial response (PR) per IWCLL 2008 criteria over the course of the study as evaluated by an IRC
	Patient-reported outcome	PRO	EORTC QLQ-30: change in scores from baseline to each assessment for all scales FACiT: Fatigue change in scores from baseline to each assessment EQ-5D: change in weighted utility score from baseline to each assessment
Results and analysis			
Analysis description	The primary analysis was a two-sided log-rank test stratified according to the presence or absence of the chromosome 17p13.1 deletion and the disease refractory status at randomisation.		
Analysis population	Inclusion	✿ patients with CLL or SLL requiring therapy if they had received at least one previous therapy and were considered to be inappropriate candidates for purine analogue treatment because they had a short progression free interval after chemoimmunotherapy or because they had coexisting illnesses, an age of 70 years or more, or a chromosome 17p13 deletion ✿ ECOG ≤ 2 ✿ absolute neutrophil count of at least 750 cells per microlitre, a platelet count of at least 30,000 cells per microlitre, and adequate liver and kidney function	
	Exclusion	✿ therapy with warfarin or strong CYP3A4/5 inhibitors	
	Characteristics		Ibrutinib vs. Ofatumumab
		Patients with SLL; %	5 vs. 4
		Median age (range); yrs:	67 (30 – 86) vs. 67 (37 – 88)
		CIRS score > 6; %:	32 vs. 32
		ECOG 0/1; %:	41/59 vs. 41/59
		Bulky disease ≥ 5 cm; %	64 vs. 52
		Chromosome 11(q22.3) del; %:	32 vs. 30
		Chromosome 17(p13.1) del; %:	32 vs. 33
		Previous therapies:	
		Median number of previous therapies (range):	3 (1 – 12) vs. 2 (1 – 13)
		≥ 3 previous therapies; %:	53 vs. 46
		Type of previous therapy; %	
		Alkylator	93 vs. 88
		Bendamustine	43 vs. 37
		Purine analogue	85 vs. 77
		Anti-CD20	94 vs. 90
		Alemtuzumab	21 vs. 17
		Allogeneic transplantation	2 vs. 1

		Median time from last therapy (range); months	8 (1 – 140) vs. 12 (0 – 184)
		Resistance to purine analogues[1]; %	45 vs. 45
Descriptive statistics and estimated variability	Treatment group	*Ibrutinib*	*Ofatumumab*
	Number of subjects	N = 195	N = 196
	Median PFS; months	NR	8.1
	PFS at six months; %	88	65
	OS at 12 months; %	90	81
	ORR; number (%) PR PR + lymphocytosis SD PD	 83 (43) 39 (20) 63 (32) 5 (3)	 8 (4) - 153 (78) 20 (10)
Effect estimate per comparison	*Comparison groups*		*Ibrutinib vs. Ofatumumab*
	PFS	HR	0.22
		95% CI	0.15 – 0.32
		P value	< 0.001
	OS	HR	0.43
		95% CI	0.24 – 0.79
		P value	0.005
	PR	OR	17.4
		95% CI	8.1 – 37.3
		P value	< 0.001
	PRO	Point estimate	NA
		Variability	NA
		P value	NA
	Subgroup analyses		
	PFS – del(17)		N = 127
		HR	0.25
		95% CI	0.14 – 0.45
		P value	NA
	PFS - refractory to purine analogues		N = 175
		HR	0.18
		95% CI	0.10 – 0.32
		P value	NA

Abbreviations: CI = confidence interval; CIRS = Cumulative Illness Rating Scale (ranging from 0 to 52, with higher scores indicating worse health status); CLL = chronic lymphocytic leukaemia; ECOG = Eastern Cooperative Oncology Group; FACIT = Functional Assessment of Chronic Illness Therapy; HR = hazard ratio; iv = intravenous; N = number; NA = not available; NR = not reached; OR = odds ratio; ORR = overall response rate; OS = overall survival, PFS = progression free survival; PR = partial response; PRO = patient-reported outcome; SLL = small lymphocytic lymphoma

[1] = defined as no response or a relapse within 12 months after the last dose of a CD20-based chemo-immunotherapy regimen that included a purine analogue.

Table 2: Most frequent adverse events (any grade ≥ 20%; grade 3 or 4≥ 5%)

RESONATE [21, 24]			
Grade (according to NCI CTC version 4.0)	**Outcome**, n (%)	**Ibrutinib** (n = 195)	**Ofatumumab** (n = 191)
Any Grade	Any adverse event	194 (99)	187 (98
	Diarrhoea	93 (48)	34 (18)
	Fatigue	54 (28)	57 (30)
	Nausea	51 (26)	35 (18)
	Pyrexia	46 (24)	28 (15)
	Anaemia	44 (23)	33 (17)
	Neutropenia	42 (22)	28 (15)
	Cough	38 (19)	44 (23)
	Infusion-related reaction	0	53 (28)
	Infections	NA (70)	NA (54)
	Bleeding-related	NA (44)	NA (12)
Grade 3 or 4	Any adverse event	99 (51)	74 (39)
	≥ 1 adverse event	NA (57)	NA (47)
	Anaemia	9 (5)	15 (8)
	Neutropenia	32 (16)	26 (14)
	Thrombocytopenia	11 (6)	8 (4)
	Pneumonia	13 (7)	9 (5)
Other	≥ 1 SAE	81 (42)	58 (30)
	Treatment discontinuation due to AEs	NA (4)	NA (4)
	Fatal AEs	NA (4)	NA (5)

Abbreviations: NA = not available; SAE = serious adverse event; AE = adverse event

RESONATE trial, phase III, compared ibrutinib to ofatumumab in 391 previously treated patients with relapsed or refractory CLL

The RESONATE trial, a phase III study, compared ibrutinib to ofatumumab in 391 previously treated patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) [21]. The median number of previous therapies was three in the ibrutinib group and two in the ofatumumab group, including alkylators, purine analogues, anti-CD20 therapies and bendamustine. The median time from the last therapy was eight months in the intervention group and 12 in the control group, but in both groups 45% of the individuals were resistant to purine analogues. All patients included had an ECOG PS of 0 or 1, and 32% in each group had a CIRS score > 6. About 60% of patients had chromosomal abnormalities, but stratification was based on the presence of chromosomal del(17p) and resistance to purine analogue chemoimmunotherapy.

hazard ratio of PFS was 0.22, favouring ibrutinib group

risk of death reduced by 57% in ibrutinib group

cross-over from ofatumumab group to ibrutinib was allowed

partial response in 43% in ibrutinib and 4% and in ofatumumab group

The median PFS, the primary outcome, was not yet reached in the ibrutinib group at a follow-up of 9.4 months, but was 8.1 months in the ofatumumab group. The hazard ratio was 0.22 (95% CI 0.15-0.32; $p < 0.001$). These benefits were also consistent in several subgroup analyses, including, for example, disease refractory to purine analogues, number of previous therapies, presence of bulky disease, chromosome deletions and Rai stage. Overall survival also yielded statistically significant improvements for ibrutinib (HR 0.43, 95% CI 0.24-0.79; $p < 0.005$). At 12 months, the overall survival rate was 90% in the intervention group and 81% in the control group. However, OS results may be influenced by the fact that approximately four months after the last patient was randomised, crossing-over to the ibrutinib group was allowed and 57 patients from the former ofatumumab group overall received the BTK inhibitor [24]. In terms of response rates, 43% in the ibrutinib

group and 4% in the ofatumumab group achieved a partial response, whereas 32% and 78% respectively had a stable disease.

serious AEs in 57% in ibrutinib group and in 47% in the ofatumumab group

Adverse events (AE) of any grade occurred in nearly all patients of both groups, and at least one serious AE was observed in 57% in the ibrutinib group, compared to 47% in the ofatumumab group. The most frequent AEs of any grade were diarrhoea, fatigue, nausea and pyrexia in the ibrutinib group, and infusion-related reactions, cough and fatigue in the ofatumumab group. Discontinuation due to AEs, as well as fatal events, were similar in both groups, but treatment exposure was 3.3 months longer in the ibrutinib group than in the ofatumumab group. Cutaneous second primary malignancies (basal-cell and squamous-cell carcinomas) were observed in 4% and 2%, and non-skin cancers in 3% and 1%. Richter's transformation, which is the development of an aggressive large-cell lymphoma out of an underlying CLL, occurred in two patients in each of the two groups.

longer treatment exposure with ibrutinib

cutaneous second primary malignancies in 4% and 2%

data monitoring committee recommended trial to be stopped

Based on the results of this interim analysis, the independent data and safety monitoring committee recommended that the trial be stopped and that any patients on ofatumumab be offered treatment with ibrutinib.

6.2 Efficacy and safety – further studies

phase Ib/II study with 85 patients assessed 420mg and 840mg

A phase Ib-II open-label study investigated ibrutinib in 85 patients overall with CLL or SLL [22]. Participants were allocated to three cohorts. The first two cohorts (27 and 24 patients) received a fixed daily dose of 420 mg of ibrutinib. Participants had received at least two previous therapies, including a purine analogue. In the third group, 32 patients received 840 mg daily until the onset of disease progression or unacceptable toxicity. This cohort was considered as high-risk patients, because they did not respond to a chemo-immunotherapy or had progressed within 24 months after completion of the regimen. 65% had advanced disease, about 70% had deletions in either chromosome 17 or 11, and the median number of previous therapies was 4. Safety in the first two cohorts was the primary endpoint. The most common AEs were diarrhoea (49%), upper respiratory tract infection (33%), fatigue (32%) and cough (31%). The most common AEs ≥ grade 3 were pneumonia (12%), dehydration (6%) and neutropenia (15%). The overall response rate was 71%, regardless of dosage. The response was not influenced by high-risk features with the exception of unmutated immunoglobulin variable-region heavy-chain gene (IGHV). Moreover, the estimate of PFS at 26 months was 75% and the OS rate 83% at a median follow-up of 20.9 months.

included were high-risk patients

most common AEs were diarrhoea, respiratory tract infection

≥grade 3 AEs: pneumonia, neutropenia

ORR: 71%

7 Estimated costs

Imbruvica® costs in Austria still unknown

Costs for Imbruvica® in Austria are not known yet.

8 Ongoing research

4 ongoing phase III trials identified for relapsed or refractory CLL patients

On http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ four ongoing phase III trials were identified for relapsed or refractory CLL patients:

- NCT01611090: to examine the safety and efficacy of ibrutinib administered in combination with bendamustine and rituximab in patients with relapsed or refractory CLL or SLL. Estimated primary completion date: August 2015.
- NCT01973387: to evaluate the efficacy and safety of ibrutinib versus rituximab in adult Asia-Pacific region patients with relapsed or refractory CLL or SLL. Estimated primary completion date: August 2015.
- NCT01724346: open-label extension study in patients 65 years or older with CLL or SLL who participated in study PCYC-1115-CA (PCI-32765 versus chlorambucil). Estimated primary completion date: June 2015.
- NCT01804686: to collect long-term safety and efficacy data for participants treated with PCI-32765 (ibrutinib) and to provide ongoing access to PCI-32765 for participants who are currently enrolled in PCI-32765 studies that have been completed according to the parent protocol, are actively receiving treatment with PCI-32765, and who continue to benefit from PCI-32765 treatment. Estimated primary completion date: January 2016.

under investigation for untreated patients and for other malignancies

Several phase III trials are ongoing on previously untreated CLL patients (NCT01722487), also in combination with other agents such as bevacizumab or rituximab (NCT01886872, NCT02048813). Several phase II studies are listed, including hairy cell leukaemia, multiple myeloma, marginal cell lymphoma, follicular lymphoma and small lymphocytic lymphoma.

9 Commentary

licensed in the US and positive CHMP decision in Europe in July 2014

Ibrutinib, a first-in-class inhibitor of BTK, was licensed under priority review by the FDA for patients with CLL who have received at least one prior therapy in February 2014 and for patients with 17p deletion in July 2014. It was the second drug that received breakthrough designation.

for CLL patients with ≥ one prior therapy, or as first-line therapy in the presence of 17p deletion or TP53

In Europe, the CHMP recently (in July 2014) formulated a positive opinion recommending to grant market authorisation for the treatment of adult patients with CLL who have received at least one prior therapy, or as first-line therapy in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemoimmunotherapy.

decisions based on RESONATE trial comprising 391 patients including del(17p)

the risk of progression or death from any cause was reduced by 78% in ibrutinib group

These decisions were primarily based on the results of the RESONATE trial, a phase III study. 391 previously treated patients were randomised to either ibrutinib orally or ofatumumab intravenously. Patients were considered unsuitable for treatment or retreatment with purine analogue-based therapy and about one-third had del(17p). At a follow-up of 9.4 months, the risk of progression or death from any cause was reduced by 78% in the ibrutinib group, a finding that was consistent in subgroup analyses including disease refractory to purine analogues, number of previous therapies, presence of bulky disease and chromosome deletions including del(17p). With a statistically significant reduction of 57% in the risk of death, OS also favoured the intervention group. In terms of response, no complete response was observed, but partial responses were experienced by 43% in the ibrutinib group, compared to 4% in the ofatumumab group.

most frequent AEs were diarrhoea, fatigue, fever

57% grade ≥ 3 AEs in ibrutinib group compared to 47% in ofatumumab group

The most frequent AEs of any grade associated with ibrutinib were diarrhoea, fatigue, fever and nausea. More patients in the ibrutinib group than in the ofatumumab group had at least one AE of grade ≥ 3 (57% versus 47%). Grade ≥ 3 AEs more commonly observed in the ibrutinib group were diarrhoea (4% vs. 2%) and irregular or rapid heart rate (3% vs. 0%). Bleeding-related AEs of any grade were also more common in the ibrutinib group than in the ofatumumab group (44% vs. 12%).

under investigation for first-line therapy and in combination with other drugs

Besides results for ibrutinib monotherapy for previously treated patients with relapsed CLL, the BTK inhibitor is already under evaluation for further indications. Phase III studies are underway, investigating its efficacy in previously untreated, sometimes including elderly CLL patients as well. Another subject of investigation is if combination therapies will increase depth of remission [25]. For example, adding cytotoxic drugs to ibrutinib may accelerate time to remission [26] and the combination with CD20 antibodies may shorten the time to response, because ibrutinib redistributes CLL cells from lymph nodes and tissue into the peripheral blood. Thus, these cells may become more sensitive to CD20 antibodies (e.g., ofatumumab) [27, 28].

development of resistance not yet understood

combination therapies may prevent resistance?

Besides the potential for improved clinical outcomes, the rationale for combination therapies rather than monotherapy with ibrutinib is to avoid the development of resistance. The mechanism is not yet understood; de-novo mutations, as well as selection from subfractions of predominantly pre-existing, malignant clones, are discussed [29]. The frequency of drug resistance to monotherapy is currently considered as low, but due to the short-follow-up, a considerable number of patients may develop resistance over time [27]. Combining therapies with different modes of action may therefore be a means for preventing resistance [30].

Richter's transformation after ibrutinib associated with poor prognosis

Another question concerns the risk of disease transformation [28]. Even though patients progressing whilst on ibrutinib therapy still respond to other available treatment options, Richter's transformation after ibrutinib is associated with a poor prognosis and only short responses have been observed on further lines of therapy [31]. In the phase III trial, however, two patients in each group experienced a transformation to an aggressive large-cell lymphoma.

continued treatment indicated

even mild/moderate AEs can compromise quality of life in the long-term

Since patients seem to respond to continued treatment and rapid tumour progression has been occasionally observed in relapsing patients after ibrutinib therapy was stopped, ibrutinib may be administered for a long period of time [25, 27], the need to further establish its side effect profile is highlighted. Unlike other available agents for CLL, the myelosuppressive potential of ibrutinib is low; therefore, diarrhoea, fatigue and nausea were side ef-

fects most often observed in the RESONATE trial [28]. These AEs were mainly mild to moderate and are considered manageable in the outpatient setting. However, in contrast to temporarily limited side effects associated with chemotherapy, these side effects can compromise quality of life in the long-term when ibrutinib is continuously used [29]. However, data regarding these outcomes are not available.

long-term side-effects of mono- and combination therapy unknown

In addition, due to the rather short observation time of ibrutinib therapy, long-term side effects are not known yet [28]. Secondary cancers, for example, occurred in the ibrutinib group in up to 4% of patients, compared to 2% in the ofatumumab group in the RESONATE trial. Lastly, it has to be determined whether a manageable side effect profile in the short- and long-term can be maintained when ibrutinib is administered in combination with, e.g., chemotherapy [29].

costs unknown but may be high especially when administered for long periods and/or in combination with other agents

Another concern is the costs for ibrutinib. No price estimates are available for Europe yet, but in the U.S., one pill costs $ 91, which adds up to $ 8,200 (≈ € 6,185) for one month of ibrutinib therapy for CLL [32]. Even though prices will likely be lower in Europe, affordability in the long-term and/or in combination with other targeted agents remains an issue [29, 30]. Therefore, monotherapy or combination therapies using ibrutinib only for a limited treatment duration may be less expensive alternatives [27, 28]. Of interest will also be the comparison of costs associated with different therapeutic strategies, considering not only established regimens but also new agents—for example, idelalisib (Zydelig®) was just approved by the FDA for recurrent/relapsed patients in July 2014, and further BTK inhibitors are in development [14, 27, 33].

new treatment options for difficult-to-treat CLL patients needed ibrutinib will soon offer a new alternative

New treatment options for CLL, primarily for difficult-to-treat patients with relapsed or refractory disease or with poor prognostic characteristics such as del(17p) or p53 mutations are needed. Foremost for these patients, ibrutinib offers an alternative.

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