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Results of a Prospective Non-Interventional Post-Authorization Safety Study of Idelalisib in Germany

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Abstract

Idelalisib demonstrated robust effectiveness and manageable safety, regardless of high-risk features, in patients with chronic lymphocytic leukemia and relapsed follicular lymphoma in routine clinical practice in Germany. This non-interventional post-authorization study supports the effectiveness and tolerability profile of idelalisib previously obtained in clinical trials.

Background: In pivotal studies, idelalisib demonstrated remarkable efficacy and manageable tolerability in patients with chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL). This prospective, multicenter, non-interventional post-authorization study assessed the characteristics, clinical management, and outcome of CLL and FL patients receiving idelalisib in routine clinical practice in Germany. **Patients:** Observational study in CLL and FL patients treated with idelalisib between September 2015 and December 2020. **Results:** A total of 147 patients with CLL and FL were included with a median age of 75 and 71 years, respectively. More than 80% of patients presented with comorbidity and many CLL patients with documented high-risk genetic features, including del(17p)/*TP53* mutation or unmutated *IGHV*. The median progression-free survival (PFS) and overall survival (OS) were not reached in the CLL cohort irrespective of del(17p)/*TP53* or unmutated *IGHV*. The estimated 6-month PFS and OS rates in CLL were 82% and 92%. The estimated 6-month PFS and OS rates for FL were 32.2% and 77.2%. Overall response rates in the CLL and FL cohorts were 70.4% and 36.4%, with the presence of high-risk genetics having no negative impact. No unexpected adverse events were observed. Most frequently reported adverse drug reactions (ADRs) were diarrhea, nausea, pneumonia, rash, and fatigue. **Conclusion:** This real-world study shows that idelalisib is an effective therapy for CLL and FL, regardless of age and high-risk genetic features, consistent with results from previous clinical trials. Collected safety data and the pattern of ADRs reflect those from previous studies.

Introduction

The phosphatidylinositol 3-kinase (PI3K) pathway plays an important role in B-cell development, proliferation, migration, adhesion, survival, and immune function.[1] Dysregulation of this pathway enables survival and retention of malignant B cells. As the

PI3Kδ isoform is selectively expressed in leukocytes, it was considered a good therapeutic target for B-cell malignancies.[2,3] Idelalisib is a first-in-class, selective, reversible, oral inhibitor of PI3Kδ, which interferes with survival mechanisms involved in hematologic cancers.[3,4] The drug was approved by the FDA and EMA in 2014 for the treatment of patients with chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL).

Current ESMO Clinical Practice Guidelines recommend the use of idelalisib in combination with rituximab to treat patients with symptomatic relapsed or refractory CLL.[5] Furthermore, idelalisib can be used as first-line therapy in the presence of del(17p) or *TP53* mutation in patients for whom no other therapies are appropriate. In patients with follicular lymphoma (FL) the ESMO Guidelines recommend idelalisib as monotherapy in double-refractory patients.[6]

Approval of the drug was based on 2 pivotal studies.[7,8] In the randomized, double-blind, placebo-controlled, pivotal phase 3 trial a combination of idelalisib and rituximab was compared to placebo and rituximab.[7] This trial included 220 patients with relapsed/refractory CLL, who were not suitable for chemotherapy, because of reduced renal function, previous therapy-induced myelosuppression, or major coexisting illness. Patients treated with idelalisib had significantly improved PFS, response rate, and OS. The 24-week PFS was 93% and 46% for the idelalisib and placebo groups, respectively, which resulted in the trial being stopped early due to treatment efficacy. The median duration of PFS was not reached in the idelalisib group and 5.5 months in the placebo group. Patients receiving idelalisib vs. those receiving placebo had improved rates of overall response (81% vs. 13%; $P < .001$) and overall survival at 12 months (92% vs. 80%; hazard ratio for death, 0.28; $P = .02$). In the single arm, open-label, pivotal phase 2 study with 125 patients with indolent Non-Hodgkin Lymphoma, 72 (58%) of those with FL, who had received a median of 4 prior therapies, idelalisib showed anti-tumor activity with an acceptable safety profile.[8,9] A retrospective post hoc analysis of this study evaluated the efficacy of idelalisib in the subgroup of patients with FL. The ORR was 57%, with 5 complete responses (13.5%) and 16 partial responses (43%). The median PFS was 11.1 months and median OS was not reached.[9]

The most common adverse reactions in patients treated with idelalisib in monotherapy and combination trials (incidence ≥12%) are fatigue, diarrhea, pyrexia, cough, pneumonia, rash, and upper respiratory infection.[10] Serious adverse events in idelalisib-treated patients included hepatotoxicity, diarrhea or colitis, pneumonitis, and infections.

Considering the importance of real-world experience in an unselected patient population, we initiated a post-authorization safety study (PASS) in Germany. In this prospective, non-interventional study, we evaluated effectiveness and safety of idelalisib as well as quality of life in patients with CLL and FL in routine clinical practice.

Patients and Methods
Study Design and Patients
This prospective, 2-cohort, multicenter, non-interventional PASS explored the safety and effectiveness of idelalisib in patients with CLL or FL in the real-world setting in Germany. Hence, inclusion of patients was based on the physician's decision to initiate treatment with idelalisib in accordance with the approved indication of the drug. The study was performed from September 2015 until December 2020 at a total of 87 sites across Germany. There were no pre-specified numbers of CLL and FL patients that had to be enrolled.

Eligible patients had to be at least 18 years of age with a diagnosis of CLL (cohort A) or FL (cohort B) and have given written informed consent. Independent ethics committees approved the study, which was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and applicable regulatory requirements. Idelalisib was administered until progressive disease, death, unacceptable toxicity, or any other reason for discontinuation or for a maximum of 36 months, whichever occurred first.

Primary end points were the rate and time to progression, overall survival, and overall response rate. Secondary end points included safety and quality of life data. Adverse drug reactions (ADRs) occurring during idelalisib treatment were described and graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 4.03.

All fatal events had to be collected. For adverse events or serious adverse events, only those considered by the investigator as related to idelalisib were collected. In case there were 2 ADR terms with equal preferred term (PT) reported per subject, the term with the highest CTCAE grade was considered for the analysis. *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and clinical and laboratory cytomegaly virus (CMV) monitoring became mandatory according to the safety update of the prescribing information in April 2016 (Amendment 3).

Methods
Descriptive statistics were used for data analysis. No statistical methods were used to replace missing values and essential missing information led to the exclusion of the study subject from the analysis set.

Time-to-event analysis including PFS and OS were estimated using the Kaplan-Meier method to present 25th and 75th percentiles of the time-to-event data together with the corresponding 95% Confidence Interval (CI) as well as the number, frequency and percentage of events and censored observations. Regarding PFS, subjects alive without disease progression at the end of the observation period were right-censored at the date of last contact or death. As for OS, subjects alive at the end of the observation period were censored at the date of last contact.

The observation period was calculated using the reverse Kaplan-Meier method. The observation period was calculated as the time from first idelalisib administration until last idelalisib administration or death.

PFS was defined as time from start of idelalisib (± other combination drug) therapy to disease progression or death of any cause. PFS rate was defined as the proportion of patients alive without disease progression 6 months, 12 months, 24 months, and 36 months from start of idelalisib therapy. Patients alive without disease progression at the end of the observation period were right-censored at the date of last contact.

Figure 1 Consort flow diagram of patient disposition. Patients with screening failure did not meet the approved indication of idelalisib.
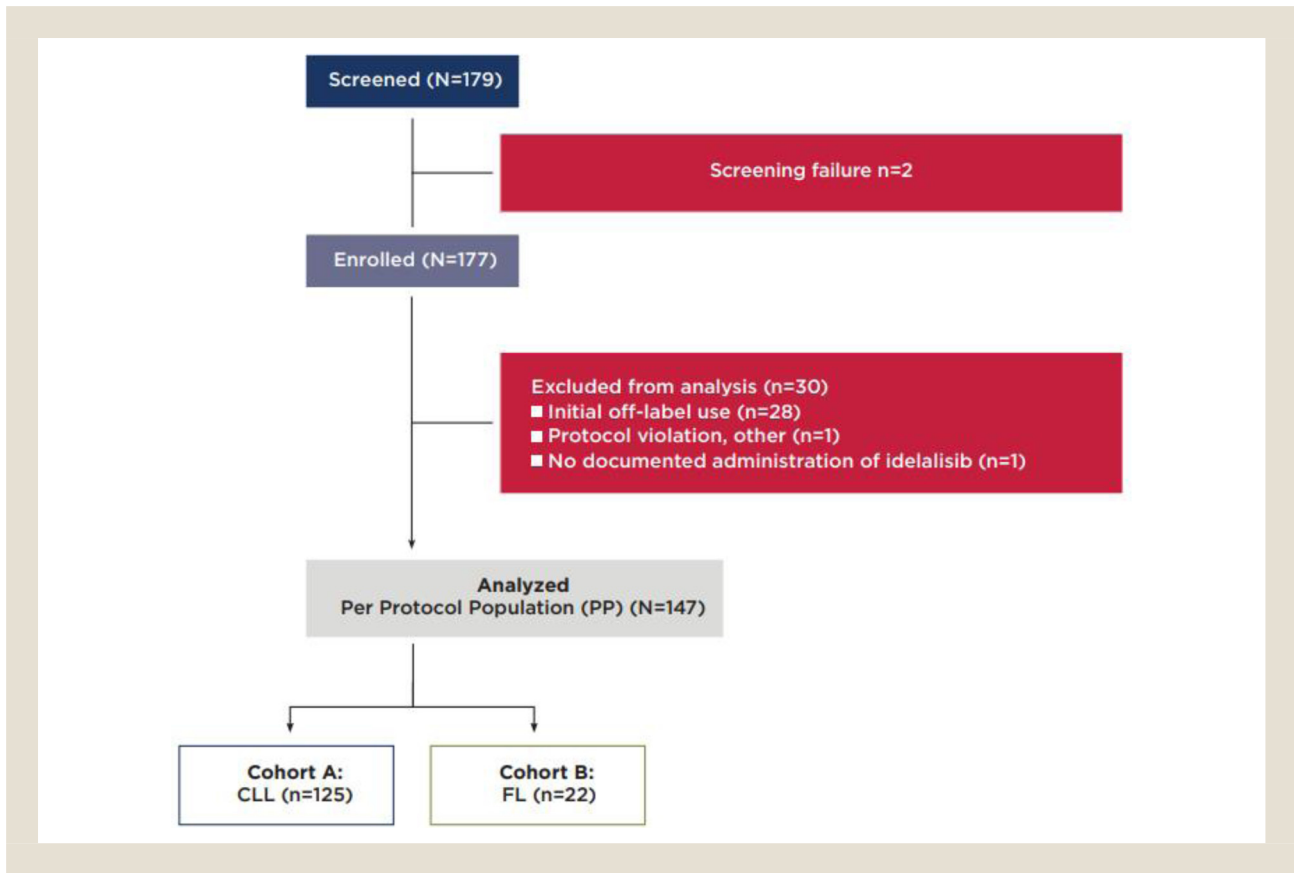
OS was defined as the time from start of idelalisib treatment to the date of death of any cause. OS rate was defined as the proportion of patients who were still alive 6 months, 12 months, 24 months, and 36 months from start of idelalisib therapy (with or without other combination drug). Patients alive at the end of the observation period were censored at the date of last contact.

The ORR was defined as the proportion of patients achieving a complete response (CR) and partial response (PR). CR was based on investigator evaluation but was not re-confirmed/assessed by bone marrow biopsy equating to non-confirmed/clinical CR. The best response to treatment was based on the investigator evaluation. Due to non-interventional design, there were no definitions given on what measures this evaluation should be based. The analysis included all subjects, including those with missing assessment of response. The ORR was additionally evaluated in a second analysis restricted to subjects with at least 1 response assessment (ORR II).

Results

Patient Characteristics

Between September 2015 and May 2020, 179 patients were screened and of these, 30 patients were excluded completely from the final analysis due to protocol violations including 28 patients with initial off-label use. There were 2 screening failures. Thus, 147

patients, 125 with CLL and 22 with FL, were analyzed in the study. In total, 87 study sites participated in the study, of these, 60 sites enrolled at least 1 subject (Figure 1).

Median age in the CLL and FL cohort was 75.0 (45-89) and 70.5 (43-92) years, respectively, with 89% and 64% of the CLL and FL patients being 65 years or older.

86% of the CLL patients and 82% of the FL patients presented with at least 1 comorbidity at baseline. 74% of CLL patients were reported with an intermediate (33% Binet stage B) or high-risk (41% Binet stage C) disease stage. Using the FLIPI score, 23% and 55% of the patients in the FL cohort were reported with an intermediate and high-risk status.

The median time from diagnosis to start of idelalisib therapy was more than 7 years (88 months) for the CLL cohort and more than 6 years (74 months) for the FL cohort (Table 1).

CLL patients had received a median number of 1 previous therapy line, 8 of these patients, all with a del(17p)/*TP53* mutation, had no prior therapy. The most common drugs used as prior therapy were bendamustine, rituximab, chlorambucil, and fludarabine either as monotherapy or in combination. Nineteen (15.2%) patients were previously treated with ibrutinib.

In the FL cohort, patients had received a median number of 2 prior lines. The most common regimens used were rituximab-bendamustine and rituximab-CHOP.

Table 1   Baseline characteristics

	CLL cohort (n=125)	FL cohort (n=22)
Median age (range)	75.0 (45.0-89.0)	70.5 (43.0-92.0)
≥ 65 years, n (%)	111 (88.8)	14 (63.6)
Gender		
female, n (%)	41 (32.8)	15 (68.2)
male, n (%)	84 (67.2)	7 (31.8)
Median time between primary diagnosis and start of idelalisib therapy (range) [months]	88.0 (0.5-330.1)	74.3 (21.3-354.9)
Karnofsky Performance Score, n (%)		
100	23 (18.4)	5 (22.7)
90	27 (21.6)	3 (13.6)
80	27 (21.6)	6 (27.3)
≤ 70	14 (11.2)	3 (13.6)
unknown	34 (27.2)	5 (22.7)
Patients with comorbidity at baseline, n (%)	107 (85.6)	18 (81.8)
Patients with prior or concomitant steroid use, n (%)	35 (28.0)	8 (36.4)
Binet stage (CLL cohort only), n (%)		
Stage A	27 (21.6)	
Stage B	41 (32.8)	
Stage C	51 (40.8)	
unknown	6 (4.8)	
Ann-Arbor classification (FL cohort only), n (%)		
Stage I		2 (9.1)
Stage II		1 (4.6)
Stage III		12 (54.6)
Stage IV		5 (22.7)
unknown		2 (9.1)
FLIPI (FL cohort only), n (%)		
high		12 (54.6)
intermediate		5 (22.7)
low		2 (9.1)
unknown		3 (13.6)
Bulky disease, n (%)		
yes	22 (17.6)	7 (31.8)
no	86 (68.8)	13 (59.1)
unknown	17 (13.6)	2 (9.1)
B symptoms, n (%)		
yes	30 (24.0)	2 (9.1)
no	91 (72.8)	20 (90.9)
unknown	4 (3.2)	0
Liver impairment *, n (%)		
yes	7 (5.6)	1 (4.6)
no	74 (59.2)	14 (63.6)
unknown	44 (35.2)	7 (31.8)
Renal impairment (CL_{Crea} < 60 ml/min), n (%)		
yes	39 (31.2)	7 (31.8)
no	51 (40.8)	9 (40.9)
unknown	35 (28.0)	6 (27.3)
Elevated LDH (> ULN), n (%)		
yes	59 (47.2)	10 (45.5)
no	53 (42.4)	12 (54.6)
unknown	13 (10.4)	0

(*continued on next page*)

Table 1	(continued)		
		CLL cohort (n=125)	**FL cohort (n=22)**
Mutational status (CLL cohort only), n (%)			
del(17p) and/or *TP53*		29 (23.2)	
IGHV unmutated		32 (25.6)	
Number of prior therapy lines, n (%)			
0		8 (6.4)	0
1		55 (44.0)	0
2		24 (19.2)	14 (63.6)
≥ 3		38 (30.4)	8 (36.4)
median (range)		1 (0-8)	2 (2-6)

* defined as bilirubin > 1.5x ULN or ALT > 2.5x ULN or AST > 2.5x ULN

Table 2	Key response data in the CLL and FL cohort and certain subgroups			
Response, n (%)	**CLL (n=125)**	**Del(17p) and/or *TP53*m CLL(n=29)**	**Unmutated *IGHV* CLL (n=32)**	**FL (n=22)**
ORR	88 (70.4)	20 (69.0)	24 (75.0)	8 (36.4)
CR	12 (9.6)	2 (6.9)	2 (6.3)	0
PR	76 (60.8)	18 (62.1)	22 (68.8)	8 (36.4)
SD	18 (14.4)	2 (6.9)	2 (6.3)	4 (18.2)
PD	3 (2.4)	3 (10.3)	1 (3.1)	5 (22.7)
Not assessed	16 (12.8)	4 (13.8)	5 (15.6)	5 (22.7)
ORR II	(n=109)	(n=25)	(n=27)	(n=17)
	88 (80.7)	20 (80.0)	24 (88.9)	8 (47.1)

Response to Treatment and Outcome

The median observation time in the CLL cohort was 10.0 months (95% CI: 7.5-12.2) with 39 (31%) censored subjects. In the FL cohort the median observation time was 6.8 months (95% CI: 3.6-8.7) with 7 (32%) censored subjects.

The median progression free survival (PFS) and overall survival (OS) in the CLL cohort were not reached. The estimated 6-month PFS and OS rates were 82.3% (95% CI: 73.5-88.3) and 91.6% (95% CI: 84.4-95.6).

Median PFS in the FL cohort was 3.5 months (95% CI: 2.3-7.7) and median OS was not reached. The estimated 6-month PFS and OS rates were 32.2% (95% CI: 13.2-52.9) and 77.2% (95% CI: 49.7-90.8) (Figures 2 and 3).

The overall response rate (ORR) in the CLL cohort (n = 88) was 70.4% (95% CI: 61.9-77.7) with a complete remission (CR) on investigator evaluation which was not re-confirmed by bone marrow biopsy (non-confirmed/clinical CR) reported in 12 (9.6%) patients and a partial remission (PR) in 76 (60.8%) patients. In the FL cohort the ORR (n = 8) was 36.4% (95% CI: 19.6-57.1). All 8 patients had a PR and none was reported with a CR (Table 2).

In those CLL patients, who had at least 1 response assessment (n = 109), the overall response rate (ORR II) was 80.7% (95% CI: 72.3-87.1). In the FL cohort (n = 17) the ORR II was 47.1% (95% CI: 26.2-69.0).

Subgroup analysis in the CLL cohort of PFS by numbers of prior regimens showed longer PFS in earlier lines of treatment (Figure 2B).

Similarly, PFS was also shorter in patients pretreated with ibrutinib, although this group was relatively small with 19 patients.

Subgroup analysis by age (<65 vs. ≥65 years), performance state (Karnofsky index < 80 vs. ≥ 80) tumor burden (bulky disease vs. not), time of relapse (early within 36 months vs. late), or by PJP prophylaxis (yes vs. no) at baseline showed similar PFS.

Similar PFS and response rates in the CLL cohort were observed independent of the presence of del(17p) and/or a *TP53* mutation. The ORR for 29 patients with del(17p) and/or *TP53*mut was 69% (95% CI: 50.63, 82.86). The median PFS for patients with these unfavorable mutations was not reached (Figure 2C).
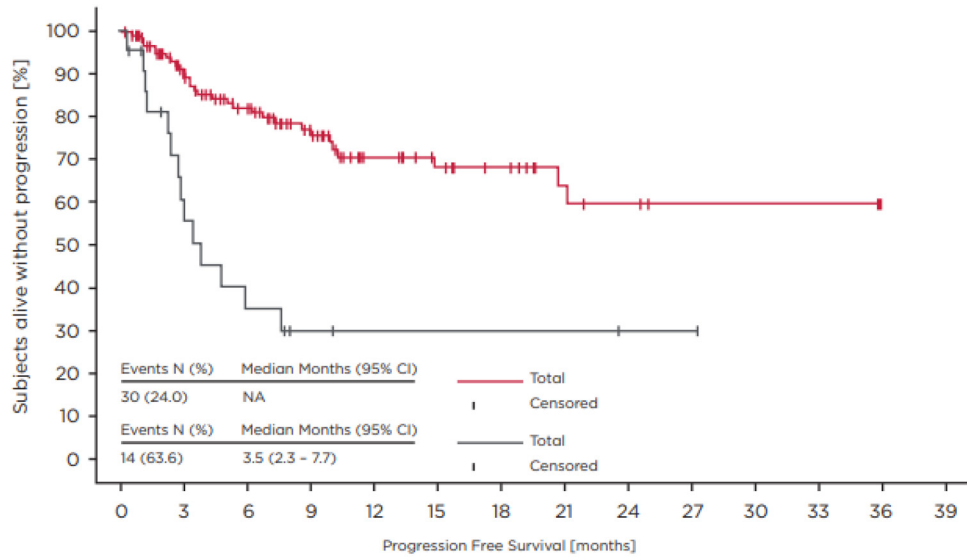
OS was longer in patients with fewer prior lines of therapies. The ORR in patients with no, one, 2 or 3 and more prior lines of therapies were 87.5%, 74.6%, 83.3% and 52.6% respectively (Figure 3B).

Safety

No unexpected adverse events were observed in these real-world cohorts. The most common reasons for the end of treatment were treatment-related AEs in 53 patients (42.7%), disease progression in 24 patients (19.4%), death in 13 patients (10.5%) and patient decision in 12 subjects (9.7%).

In total, 184 adverse drug reactions (ADRs) were documented in 82 CLL and 11 FL patients. Of these, 52 patients (CLL: n = 48; FL: n = 4) had at least 1 serious ADR (73 events in total), including 7 patients with fatal outcome (CLL: n = 6; FL: n = 1). Fatal SADRs included the following nine events: urinary tract infection, multiple organ dysfunction syndrome, diarrhea, bronchopulmonary aspergillosis, febrile neutropenia, pneumonia, pneumonitis, disease progression, and Richter transformation. The
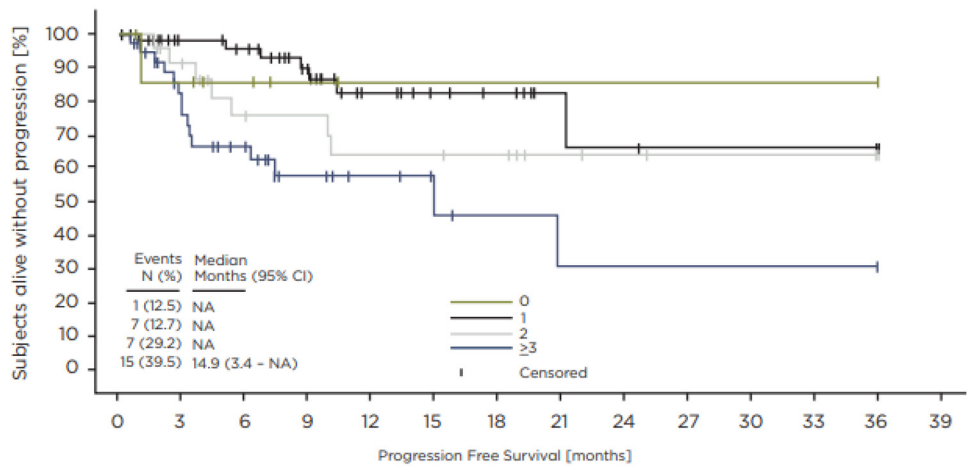
Figure 2 | **Continued**

most frequently reported ADRs were diarrhea, pyrexia, pneumonia, fatigue, increased liver enzymes (AST and ALT), leukopenia and neutropenia.

Forty-six (31.3%) patients were reported with diarrhea/colitis, 17 (11.6%) with a serious condition. The diarrhea/colitis was resolved in 30 (20.4%) subjects.

In total, 82 (65.6%) CLL patients were reported with ≥1 ADR (highest CTCAE severity grade). The most frequently (≥3 subjects) reported ADRs (PT) were diarrhea (n = 35; 28.0%), pyrexia (n = 6; 4.8%), pneumonia (n = 5; 4.0%), alanine aminotransferase increased, fatigue, leukopenia, neutropenia, neutrophil count decreased (each n = 4; 3.2%), aspartate aminotransferase increased, and pruritus (each n = 3; 2.4%).

In FL a total of 11 (50.0%) patients were reported with ≥1 ADR (highest CTCAE severity grade). The most frequently (≥2 subjects) reported ADRs (PT) were diarrhea (n = 8; 36.4%), rash (n = 3; 13.6%), and nausea (n = 2; 9.1%).

As recommended in the prescribing information for idelalisib, 114 (77.6%) of patients received PJP prophylaxis at baseline. 112 patients received TMP/SMX. Dapsone (n = 1) and pentamidine IV (n = 1) was administered after intolerance to TMP/SMX. 33 (22.4%) patients (24 CLL; 9 FL) had no PJP prophylaxis at baseline. Four of these (3 CLL; 1FL) started PJP prophylaxis later during idelalisib treatment. For 3 CLL patients with no PJP prophylaxis at baseline, lung-related ADRs were reported (pneumonitis CTCAE severity grade 3 (n = 1), PJP CTCAE severity grade 3 (n = 1), pneumonia CTCAE severity grade 5 (n = 1).

Dose Reductions and Treatment Interruptions

According to the prescribing information, treatment with idelalisib should be continued until disease progression or unacceptable toxicity and may continue for several months or years. Optimal therapy management is therefore important and may include temporary treatment interruptions (TIs) and dose modifications to manage idelalisib associated adverse drug reactions (ADRs).

Twenty-eight patients had idelalisib dose reductions during the study due to inacceptable toxicity or (serious) adverse events with no drug relation suspected, 22 in the CLL group and 6 in the FL group. Of those, most cases (n = 22) were adverse drug reactions (ADR) and in 6 cases no idelalisib relation was suspected.

Thirty-eight CLL (30.4% of the CLL cohort) and 5 FL patients (27.3% of the FL cohort) had at least 1 temporary TI and resumed idelalisib therapy thereafter (Figure 4). Of these, 8 patients (7 with CLL, 1 with FL) had 2 and 2 CLL patients had 3 TIs. The duration of the respective TIs varied widely from 1 to 235 days. The median duration of these temporary TI was 15 days. Of all patients with a TI, fifteen had at least 1 interruption with a duration of >30 days.

Nineteen patients (17 in the CLL group and 2 in the FL group) resumed therapy with a reduced idelalisib dose after 24 episodes of TI. Patient level data suggest that lymphocyte and leukocyte counts were relatively stable during and after TIs irrespective of cytogenetic aberrations.
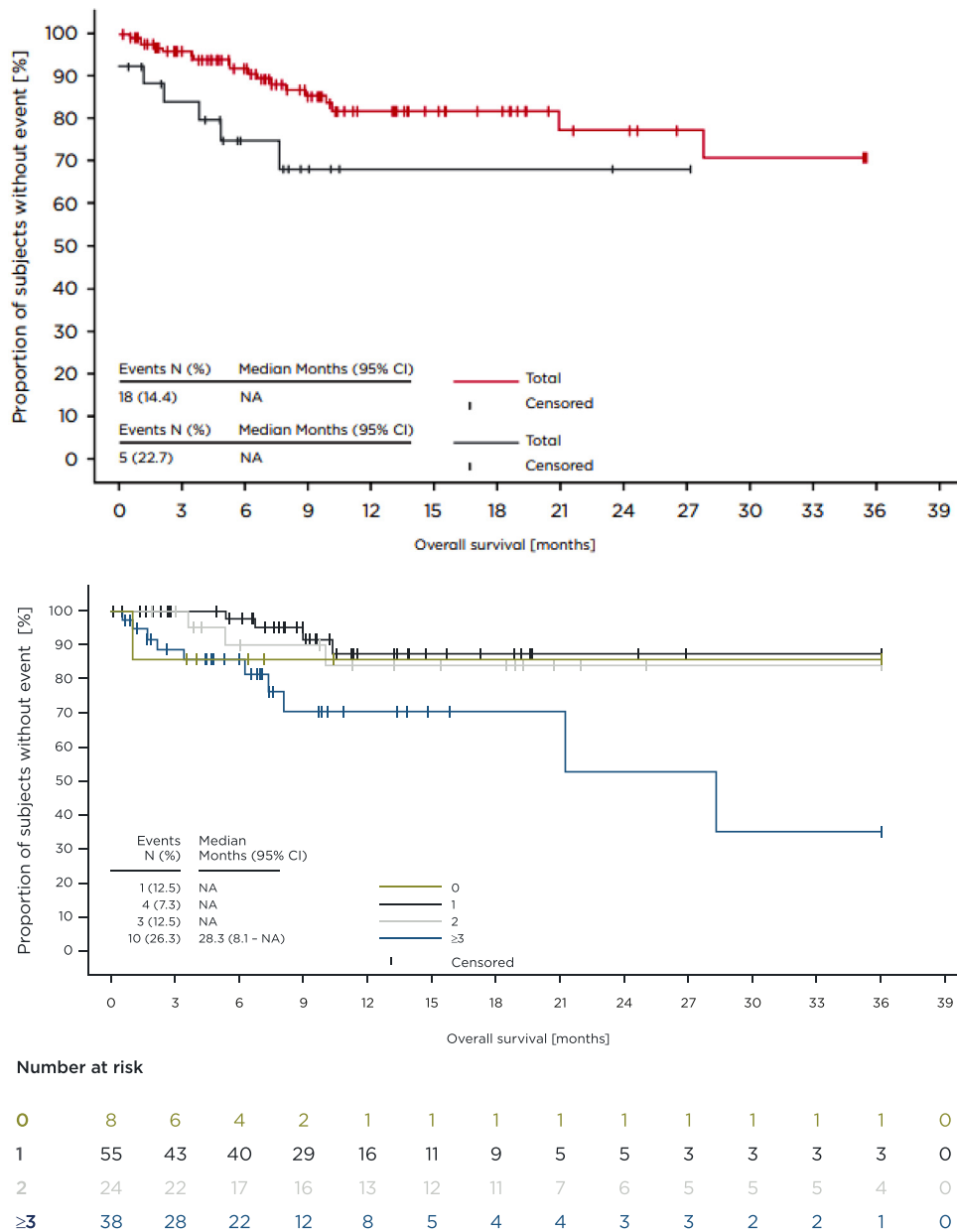
Discussion

This prospective real-world PASS aimed to assess the characteristics, clinical management, and outcomes of CLL and FL patients receiving idelalisib under routine clinical practice conditions in Germany. To our knowledge, this is the first real-world-study that was exclusively conducted in Germany.

Idelalisib, approved for both entities FL and CLL, belongs to a list of medicines authorized in the EU that are being monitored particularly closely by regulatory authorities. The IDELA PASS assesses effectiveness and safety of both indications and reports ADRs frequencies and management.

Previous real-world analyses showed similar effectiveness and safety profile to those from the registrational studies of idelalisib in patients with CLL and FL.[11,12,13]

Interestingly, although more alternative chemo-free treatment options are available in CLL in comparison with FL, 5 times more CLL patients were enrolled and eligible for analyses than FL patients.

Figure 4 Patient based treatment interruption analysis. The figure shows in each case the number of treatment days with full and reduced idelalisib dose as well as the duration of therapy interruptions.
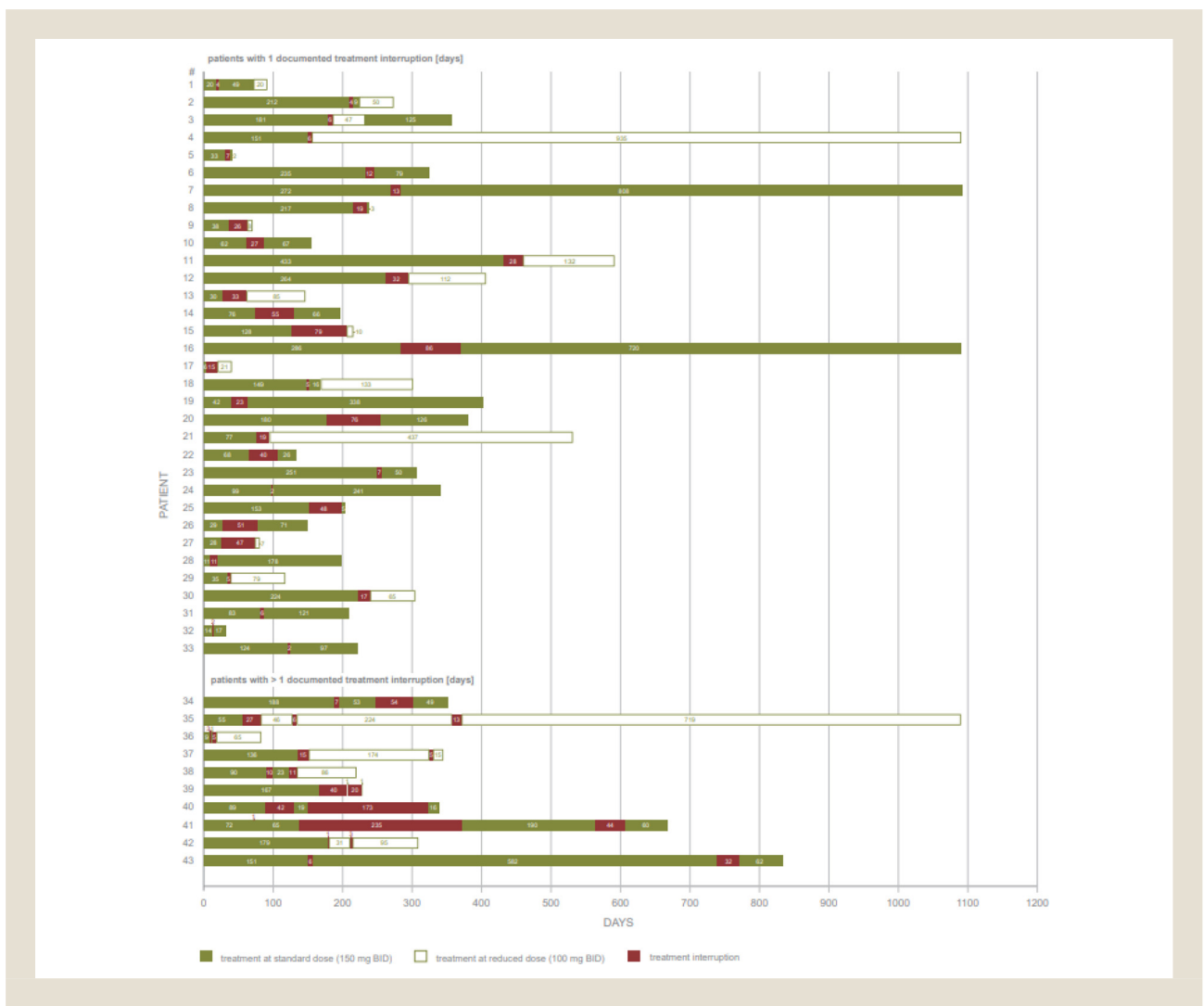
Off-label use of idelalisib, mainly as monotherapy without rituximab in CLL, resulted in a high drop-out rate of 23%. This was also described in other real-world cohort studies and may have been influenced by promising results from phase 1 monotherapy trials of relapsed and refractory CLL.[14,15]

Median age in the CLL cohort was 75 years, which corresponded to the average age for this disease and was consistent with a recently published cohort of Medicare beneficiaries with CLL,[14] that reported a median age of 76 years, which was also higher as the reported median age of 71 years in the pivotal Study 312-0116.[7]

Surprisingly, although randomized studies for treatment of relapsed/refractory CLL show higher ORR and better PFS for venetoclax in combination with rituximab or ibrutinib as monotherapy or in combination with BR[16,17,18] in comparison to idelalisib and rituximab, only 20 patients had ibrutinib or venetoclax-based pretreatments. 44% of CLL patients received idelalisib early in the disease course. Treatment-related safety concerns like tumor lysis syndrome and hospitalization (venetoclax) or atrial fibrillation or bleeding complications (ibrutinib) may in part explain the preferential enrolment in this study of this older and more ill cohort, where 86% had comorbidities of relevant concern. Of note, current ESMO guidelines recommend idelalisib and rituximab still as alternative third-line option after BTKi or venetoclax.[5]

Both, median PFS and median OS were not reached by end of the study, neither for the entire CLL cohort nor for patients with documented *TP53* aberrations (23% with del(17p) and/or *TP53*mut). The ORR and ORR II in the CLL cohort were 70% and 81%, respectively, which is similar to the response rates seen in the pivotal clinical trial.[7] Although these results are subject to limitations, they confirm the efficacy of idelalisib reported previously in clinical studies. This includes the efficacy in high-risk CLL patients with *TP53* aberrations, suggesting that idelalisib may reverse the poor prognosis of CLL patients with certain genetic alterations.[20,21]

As expected, patients with fewer prior therapies had longer PFS and OS. Otherwise, patients responded comparably well to treatment with idelalisib regardless of age, general condition, tumor burden and time of relapse.

Idelalisib has been registered in double-refractory FL and is recommended for later relapsed FL patients with high tumor burden as monotherapy in palliative intent.[6] Although median OS was not achieved in the FL cohort, median PFS of 3.5 months was short compared to 11.1 months previously published study data on idelalisib monotherapy in FL patients.[9] Furthermore, none of the FL subjects achieved a complete remission and the ORR of 36% (ORR II, 47%) was lower than the reported 57% in the pivotal clinical trial.[8,9] However, these results must be interpreted with caution due to the small number of FL subjects (n = 22) and the high number of censored cases. Further subgroup evaluations did not appear meaningful due to the small number of patients.

No new safety signals and no unexpected idelalisib-related adverse events were reported in this observational study. Concerning the frequency of ADRs, particular attention should be paid to diarrhea/colitis. These side effects associated with idelalisib are usually reversible and can be treated effectively if addressed early after their onset.[22] It is therefore recommended that health care professionals advise patients and caregivers that diarrhea of any type while taking idelalisib should be noted and treated as soon as possible.

In 2016, risk minimization measures to prevent infection in patients treated with idelalisib, regardless of indication, have been updated with further guidance regarding Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus infection. Although no survival benefit was ultimately shown for those patients who received PJP prophylaxis at baseline (77.6%), there is a strong recommendation to administer PJP prophylaxis to all patients treated with idelalisib.[5,6]

The main reason for end of treatment were side effects in 43% of patients. This indicates that therapy management and management of ADRs is important so that more patients could benefit longer from idelalisib therapy. Instead of permanent discontinuation of idelalisib treatment, dose modification as well as temporary interruption of therapy may be an option to address idelalisib associated ADRs. The small number of patients who resumed treatment with idelalisib after interruptions in therapy of varying lengths showed that this did not result in rapid disease progression. Retrospective data from 125 indolent lymphoma patients and 283 CLL patients confirmed our findings and showed that patients who experienced interruptions had a statistically significant PFS (lymphoma) and OS (CLL) benefit.[19] This indicates that idelalisib therapy may be interrupted for a time that allows treatment of ADRs or other adverse events and that subsequent resumption of idelalisib therapy is possible.

While a clinical trial in CLL patients treated with idelalisib and rituximab showed a significant improvement in quality of life vs. placebo plus rituximab, these results could not be confirmed in this real-world study.[23] This was probably due to the high number of drop-outs, incomplete questionnaires and the fact that there was no comparison arm. At least, the results of patient reported outcomes from this study do not indicate a significant worsening of health-related quality of life with idelalisib treatment.

Overall, the number of patients enrolled in this study fell significantly short of initial expectations. Possible reasons for this are that new therapy options and new therapy standards for CLL emerged during the course of the study with the approval of ibrutinib, obinutuzumab and venetoclax. In addition, clinical trials offered further therapeutic options for patients with CLL and FL.

Generalizations from a real-world observational study are limited and there was no follow-up of patients once they dropped out of the study. Nevertheless, this study in a broader and less selected patient population compared to subjects included in clinical trials supports efficacy and tolerability data previously obtained in pivotal trials.

Conclusion

This real-world study shows that idelalisib-based treatment is an effective option in CLL and FL patients, regardless of age, performance stage, tumor load and high-risk genetic features, in line with clinical trials. With the approval of second generation BTK inhibitors with improved safety profile, we see idelalisib and rituximab still as a chemotherapy-free option in third-line CLL treatment. In follicular lymphoma, PI3K inhibitors are available as options in third-line FL, especially for patients, ineligible for transplantation or CAR-T cells.

This study also supports that idelalisib has a manageable safety and tolerability profile, with no unexpected safety issues. Compliance with PJP prophylaxis in addition with monitoring of CMV reactivation and optimal management of immune-related ADRs including appropriate and timely dose interruptions and reductions of idelalisib until recovery are strongly recommended to improve effectiveness and tolerability and may increase the benefit especially in an older, pretreated patient population with frequent concomitant diseases.

Clinical Practice Points

- This study describes extensive real-world data on the use of idelalisib in CLL and FL, therefore providing valuable data on prescription patterns of this targeted agent in Germany.
- Data supports the effectiveness of idelalisib, regardless of age, performance stage, tumor load, time of relapse and high-risk molecular features, in line with clinical trials. The PFS and OS benefit was observed across all patient subgroups defined by clinical and molecular risk factors.
- The robust effectiveness of idelalisib has been demonstrated regardless of high-risk genetic features in chronic lymphocytic leukemia, including del(17p)/TP53 mutation, and unmutated IGHV.
- The reported safety profile was consistent with side effects observed previously in clinical trials. Most common adverse drug effects were diarrhea, nausea, pneumonia, rash and fatigue.
- Treatment interruptions and dose reductions are recommended options to manage adverse drug reactions. Observation of the respective patients who resumed idelalisib therapy after treatment interruption suggest that such a pause does not immediately lead to disease progression.

Author Contributions

M. A. Hoechstetter: Design of the study, acquisition of data, data analysis and interpretation, manuscript preparation and review. W. Knauf: Design of the study, data analysis and interpretation, manuscript preparation and review. W. Abenhardt and M. Rummel: Design of the study, acquisition of data, data analysis, interpretation, and manuscript review. A. van Troostenburg and H. Ramroth design of the study, data analysis and interpretation, manuscript preparation and review. S. Dambacher and K. Höhne: Data analysis and interpretation, manuscript preparation, and review. N. Hucke: acquisition of data, data analysis and interpretation, manuscript preparation, and review. All authors read and approved the final version of the manuscript.

Disclosure

M. A. Hoechstetter: Speaker fees, trainings, travel grants and participation in advisory boards from Gilead, Abbvie, Janssen, AstraZeneca, Bayer. W. Knauf: Speaker fees and participation in advisory boards from AbbVie, Amgen, AstraZeneca, Beigene, BMS, Celgene, Gilead, Janssen, Pfizer, Roche, Sanofi. S. Dambacher, A. van Troostenburg, H. Ramroth, K. Höhne and N. Hucke are Gilead employees. W. Abenhardt and M. Rummel have nothing to declare.

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