Combined therapy with ibrutinib and bortezomib followed by ibrutinib maintenance in relapsed or refractory mantle cell lymphoma and high-risk features: a phase 1/2 trial of the European MCL network (SAKK 36/13)

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Summary

Background The Bruton's tyrosine kinase inhibitor ibrutinib and the proteasome inhibitor bortezomib have single-agent activity, non-overlapping toxicities, and regulatory approval in mantle cell lymphoma (MCL). In vitro, their combination provides synergistic cytotoxicity. In this investigator-initiated phase 1/2 trial, we established the recommended phase 2 dose of ibrutinib in combination with bortezomib, and assessed its efficacy in patients with relapsed or refractory MCL.

Methods In this phase 1/2 study open in 15 sites in Switzerland, Germany and Italy, patients with relapsed or refractory MCL after ≤2 lines of chemotherapy and both ibrutinib-naïve and bortezomib-naïve received six cycles of ibrutinibb and bortezomib, followed by ibrutinib maintenance. For the phase 1 study, a standard 3 + 3 dose escalation design was used to determine the recommended phase 2 dose of ibrutinib in combination with bortezomib. The primary endpoint in phase 1 was the dose limiting toxicities in cycle 1. The phase 2 study was an open-label, single-arm trial with a Simon's two-stage min–max design, with a primary endpoint of overall response rate (ORR) assessed by CT/MRI. This study was registered with ClinicalTrials.gov, NCT02356458.

Findings Between August 2015 and September 2016, nine patients were treated in the phase 1 study, and 49 patients were treated between November 2016 and March 2020 in the phase 2 of the trial. The ORR was 81.8% (90% CI 71.1, 89.8%, CR(u) 21.8%) which increased with continued ibrutinib (median 10.6 months) to 87.3%, (CR(u) 41.8%). 75.6% of patients had at least one high-risk feature (Ki-67 > 30%, blastoid or pleomorphic variant, p53 overexpression, *TP53* mutations and/or deletions). In these patients, ibrutinib and bortezomib were also effective with an ORR of 74%, increasing to 82% during maintenance. With a median follow-up of 25.4 months, the median duration of response was 22.7, and the median PFS was 18.6 months. PFS reached 30.8 and 32.9 months for patients with a CR or Cru, respectively.

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Interpretation The combination of ibrutinib and bortezomib shows durable efficacy in patients with relapsed or refractory MCL, also in the presence of high-risk features.

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Keywords: Mantle cell lymphoma; High risk biology; Ibrutinib; Bortezomib

Research in context

Evidence before this study

In 2013, when this study was designed, there was no standard therapy for patients with relapsed mantle cell lymphoma (MCL). Allogeneic stem cell transplants were preferred in young and fit patients, and older patients preferably received single agent systemic therapy. Options included rituximab, bortezomib, lenalidomide, thalidomide, gemcitabine, fludarabine, chlorambucil, bendamustine, cladribine, and mTOR inhibitors. Responses were of short duration. In November 2013, ibrutinib was approved by FDA and by the EMA, and in Switzerland in autumn 2014. When the results on the efficacy of ibrutinib were first reported, the overall response was 66% with a complete remission rate of 17%, the median duration of response was 17.5 months, and the median progression-free survival was 13.9 months. In contrast to the US where bortezomib was approved in 2006 (Switzerland: 2009) for patients with relapsed MCL, this drug was not approved in the EMA region until 2015. In patients with relapsed MCL, the reported overall response rates reached up to 50%, with a median PFS up to 5.6 months. The limiting toxicity of the intravenous infusion of bortezomib is peripheral neuropathy. Attempts to increase its tolerability included a subcutaneous administration. In contrast to multiple myeloma, weekly bortezomib monotherapy was shown to be inferior to bi-weekly administration. The rationale to combine ibrutinib and bortezomib in this trial was based on the demonstration of a synergistic interaction of ibrutinib in both bortezomib-sensitive and refractory MCL cells, and the known non-overlapping toxicities of the two drugs. PubMed searches in 2014 and 2015 using the search terms "ibrutinib", "bortezomib", "mantle cell lymphoma", and information by Janssen found no published evidence on the combination of ibrutinib and bortezomib. A combination of bortezomib and idelalisib was not feasible, and trials of ibrutinib with either bendamustine (NCT01886872) or temsirolimus (NCT01646021), or ibrutinib monotherapy in patients previously exposed to bortezomib (NCT01599949) had already been launched.

Added value of this study

Our study showed that the combination of ibrutinib at the dose of 560 mg daily and twice-weekly subcutaneous bortezomib at 1.3 mg/m^2 is overall safe. During the accrual period of this trial, the impact of biological features of MCL on treatment outcomes became a major focus. We therefore complemented our efficacy results with a comprehensive and exploratory analysis of biological high-risk features in MCL. Currently, this information is limited or not yet available for recently launched trials, or if available shows considerably decreased efficacy in this population. Our trial reveals that combination of ibrutinib and bortezomib has durable efficacy in patients with relapsed or refractory MCL, also in presence of biological high-risk features.

Implications of all the available evidence

With frequent relapses, patients with high-risk MCL pose a major challenge to achieve long-term disease control. The field of MCL is evolving through better understanding of MCL pathology. The relatively low benefit of combinations with bendamustine and ibrutinib or newer drugs such as lenalidomide, venetoclax and rituximab in the first line, or ibrutinib and venetoclax in the relapsed setting for the high-risk population is intriguing. Despite its non-randomised design, the current study provides evidence for an effective therapeutic option for patients with relapsed and refractory MCL with high-risk features, the populations with greatest need. Furthermore, this investigator-initiated trial provides evidence on this combination, and proposes it as a comparator for future informative phase III trials. The latter will ideally include appropriate biomarkers and translational research.

Introduction

Mantle cell lymphoma (MCL) is a distinct lymphoma entity representing ~5% of all lymphomas, typically at advanced stages, with a median age at presentation of 60–70 years, and a 70% preponderance in males.[1] The clinical course of MCL is highly variable ranging from an indolent disease to a rapidly progressive disease, and the overall median survival is ~5 years. MCL currently

remains incurable, as almost all patients will eventually relapse after first-line treatment and require subsequent therapy. The disease-free survival is progressively shorter with each subsequent relapse, thus new therapeutic options are needed.

The first-in-class oral and irreversible Bruton tyrosine kinase (BTK) inhibitor ibrutinib is an approved and preferred standard option for patients with MCL, especially with early relapsed or refractory disease.[2–4] Data on its efficacy and safety with up to 9.7 years of follow-up and pooled from three clinical trials demonstrate a median progression-free survival (PFS) of 10.3 months in patients having received >1 prior line of therapy, and 67.7 months in patients reaching a complete remission (CR).[4] With an overall response rate (ORR) of 66.8%, CR is achieved in 24% in this population. By reversibly inhibiting the β5 subunit, bortezomib belongs to the class of proteasome inhibitors. The inhibition disrupts protein homeostasis and leads to rapid accumulation of cytosolic poly-ubiquitinated proteins at the endoplasmic reticulum (ER) membrane triggering an ER stress response, and cell death through transcriptional activation of NOXA.[5] In the PINNACLE trial, the response rate of single agent bortezomib in relapsed or refractory MCL was 31%, and the duration of response 9.2 months.[6]

Patients with mutated *TP53* have a more aggressive disease course and a poorer outcome with both traditional and intensive chemoimmunotherapies.[7,8] Responses to monotherapy with ibrutinib are also less favorable, and with no CRs compared to 23% of the overall population after >1 prior lines. Besides *TP53* aberrations (overexpression, mutations and locus deletions), the pathobiological definition of a high-risk MCL includes the blastoid/pleomorphic histology, a high-risk simplified and combined mantle cell lymphoma international prognostic index (MIPI) and a Ki-67 index of ≥30%.[9] Co-administration of ibrutinib and bortezomib was shown to increase proteasome inhibitor activity synergistically in MCL cells that are either sensitive or resistant to bortezomib.[10] These findings, along with the reported single agent activities and the non-overlapping toxicities, were the rationale to combine ibrutinib and bortezomib in this investigator-initiated trial.

Methods

Patient population, treatment, and ethics

Patients were eligible with a centrally confirmed diagnosis of MCL relapsed or refractory after ≤2 lines of chemotherapy (incl. high-dose chemotherapy). In December 2016, the protocol was amended from a maximum of two previous treatment lines to any prior treatment line. Patients with prior ibrutinib or bortezomib therapy, with CNS disease, neuropathy from prior therapy grade ≥2 (according to CTCAE criteria Version 4.0) at registration, and due to concerns of pharmacological interactions with ibrutinib patients in need of anticoagulation, or active hepatitis B, C or HIV infection were excluded. Patients had to have at least one measurable lesion by CT/MRI.

Nine patients in the phase 1 part were recruited from August 2015 to September 2016 in 4 Swiss sites, and from November 2016 to March 2020 49 patients in additional 11 sites in Switzerland, Germany, and Italy. Bi-weekly bortezomib was previously shown to be superior to the weekly administration.[11] 55 patients, therefore, received six 21-days cycles of daily 560 mg ibrutinib and subcutaneous bortezomib 1.3 mg/m^2, days 1, 4, 8, 11 q3w, followed by daily 560 mg ibrutinib maintenance until progression or unacceptable toxicity and were included in the efficacy analysis. After a protocol amendment in December 2016, the combination therapy was reduced to a minimum of 4 cycles to decrease its possible toxicity. All institutional review board/ethics committees of participating centres approved the study (Swissmedic 701226, BASEC Lead EC Bern PB_2016-00556).

All patients provided written informed consent before enrollment. The study followed the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and local regulations. The protocol and the amendments are provided in the Supplemental materials. This study was registered with ClinicalTrials.gov, NCT02356458.

Study design and endpoints

For the phase 1 study, a standard 3 + 3 dose escalation design to determine the recommended phase 2 dose (RP2D) of ibrutinib in combination with bortezomib was applied. The primary endpoint in phase 1 was the dose limiting toxicities in cycle 1. A fixed dose of bortezomib was used with two different dose levels (DLs) of ibrutinib 420 mg daily for 21 days (dose level 1), and 560 mg (dose level 2). The RP2D was defined as the dose level in which ≤1 of 6 patients developed a dose-limiting toxicity (DLT). DLTs were assessed in cycle 1 and were defined as study drug-related adverse events (AE, CTCAE, v4.0) including ≥7 missed days of ibrutinib, ≥2 missed doses of bortezomib, a delay of >2 weeks of cycle 2, haematological DLTs (ANC <0.5 for ≥7 consecutive days, febrile neutropenia, and G4 thrombocytopenia), and non-haematological AEs ≥ G3. The use of haematopoietic growth factors (e.g., granulocyte-colony stimulating factor (G-CSF)) during cycle 1 was only allowed after the patient experienced a DLT. Phase 2 was an open-label, single-arm trial with a Simon's two-stage minmax design. The primary endpoint in the phase 2 part was overall response (OR) defined as the best response during combination therapy (after start of trial treatment up to 21 days after end of last cycle with both trial drugs), based on CT/MRI (*Cheson, 1999*).[12] OR

was defined as either CR, complete remission unconfirmed (CRu) or partial response (PR). Secondary endpoints included AEs until 30 days after trial treatment, overall response based on best response during trial treatment (combination & maintenance therapy), duration of response (DoR), and progression-free survival (PFS). Collection of data on the secondary endpoints was terminated on 30 March 2021 by the SAKK Board due to financial restrictions of the organisation at this time.

Determination of the p53 status

Immunohistochemistry

This analysis was performed using an automated Ventana benchmark stainer using the DO-7 clone (prediluted, Roche-Ventana, Tuscon, AZ, USA). Only nuclear positivity of p53 was counted.

FISH

For the analysis of *TP53* deletions by fluorescence *in situ* hybridisation, the ZytoLight ® SPEC TP53/CEN 17 Dual Color Probe (ZytoVision, Bremerhaven, Germany) was applied. This probe marks both the *TP53* locus and the centromere of chromosome 17 (CEP17). The case was categorised as *TP53* locus deletion when the ratio of the *TP53*-locus signals to the Cep17 signals is <0.81. A total of 47 cases could be analyzed by FISH.

Next generation sequencing

Only biopsy samples with a tumour cell content >10% were considered eligible for Next Generation Sequencing (NGS). Analysis for *TP53* mutations by NGS was performed using IonAmpliseq customised TP53 panel (#A47564 Thermo Fisher Scientific, Waltham, MA, USA) on The Ion Torrent™ Genexus™ Integrated Sequencer (ThermoFisher Scientific). In 39 cases, NGS yielded analysable results. Only mutations with a variant allelic frequency of >5% were considered.

Statistical analysis

No formal sample size calculation was performed for the phase 1. For Phase 2, a Simon two-stage design (minimax) was used. An overall response of 65% or less was considered clinically not relevant (*P0*) and 80% or higher was considered as promising (*P1*). With an alpha of 5% (one-sided) and a power of 80%, a total of 55 evaluable patients were required. Reporting of two-sided 95% CI for the primary endpoint ORR was planned for in the protocol. However, the study was design assuming a one-sided alpha of 0.05. Therefore, two-sided 90% CI was deemed more meaningful at the time of writing the statistical analysis plan and the manuscript. The patients from Phase 1 who were treated at the RP2D of ibrutinib contributed to the number of patients for phase 2. One interim analysis for safety (n = 16 patients) and one for efficacy (n = 31) were performed during phase 2. All efficacy analyses were based on the phase II full analysis set, defined as all patients registered in phase 2 and patients from phase 1 treated with the RP2D. All safety analyses were based on the phase 2 safety analysis set defined as all patients who received any dose of trial treatment. For the primary endpoint, the OR rate and two-sided 90% Clopper-Pearson CI was calculated. Otherwise, summary statistics presented were the median and the range for quantitative, and counts and percentages of patients in each category for categorical variables. Time-to-event endpoints were summarised by the median and corresponding 95% confidence interval (CI) using the Kaplan–Meier (KM) method. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC) and R v4.0.3 (Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funders, including Janssen (provided the study drugs), had no role in the study design, data collection, data analyses, interpretation, or writing of the report.

Results

Between August 2015 and March 2020, 58 patients were enrolled (see Fig. 1). The baseline characteristics of the 55 patients assessed in the efficacy analysis (including 6 patients from phase 1 who received ibrutinib at the RP2D dose of 560 mg) are summarised in Table 1. The median age was 71 years (range 47–90), with an

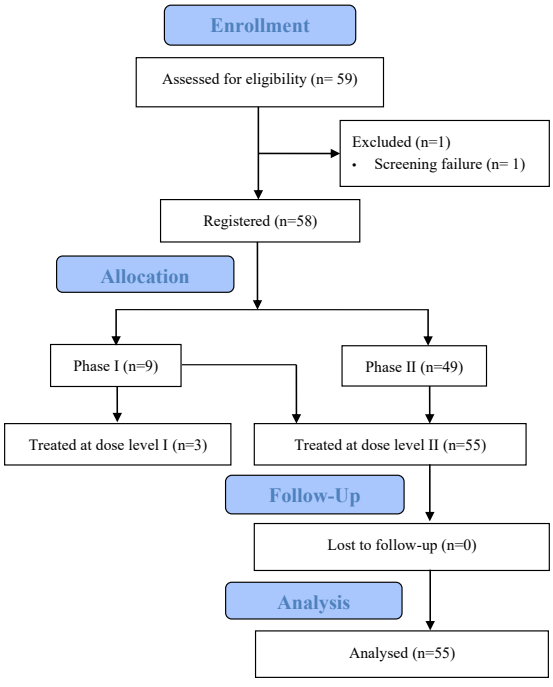

***Fig. 1:* Flowchart of study population**. Patients assessed for the efficacy analysis (primary endpoint of the phase 2 part of the trial).

	n = 55
Median age, years (range)	71 (47–90)
Male	43 (78%)
Female	12 (22%)
ECOG	
0	41 (75%)
1	14 (25%)
Previous lines of therapy	
1	35 (63.6%)
2	15 (27.3%)
3	3 (5.5%)
4	–
5	2 (3.6%)

Abbreviation: Eastern Cooperative Oncology Group (ECOG) Performance status scale.

Table 1: **Characteristics of patients in the cohort of the efficacy determination.**

expected male preponderance of 78%. ECOG was 0 in 75% of patients. In December 2016, the protocol was amended from a maximum of two previous treatment lines to any prior treatment line. When entering the trial, two third of patients (63.6%) had received one prior line; intensive induction and high-dose consolidation was counted as one line. High-dose chemotherapy with BEAM and autologous stem cell transplantation had been given in 16/55 (29%) of patients. The pretreatment of the remaining 20 (of 55, 36.6%) patients consisted of up to 5 prior lines.

Phase 1

No patient experienced a DLT during the first cycle, i.e., the minimum of 9 patients was needed to determine that whether 560 mg daily is the RP2D of ibrutinib in combination with bortezomib.[13] Most frequent adverse events (AE) of the combination treatment were thrombocytopenia (9 patients), peripheral polyneuropathy (PNP), fatigue and anaemia (6 patients each), diarrhea and injection site reaction (5 patients each). The majority of AEs were graded G1 and G2. Six patients experienced grade 3 AEs including thrombocytopenia (3 patients), PNP (3 patients), lung infections, lymphocyte count decreased (2 patients), and one patient had a grade 4 thrombocytopenia. Although considered grade 1–2, an unexpected AE in 5 patients was an injection site reaction. In a protocol amendment, 8 mg dexamethasone was allowed as co-medication prior to the subcutaneous injecting of bortezomib.

Toxicities of ibrutinib and bortezomib in phase 2

During phase 2, we did not observe new safety signals compared with phase 1. Adverse events were seen in all patients, with a grading of 3 in 67.3% and 4 in 21.8%. The most frequent toxicities were grade 1 or 2 diarrhea (36%), grade 3 infections (25%, mainly pulmonary), and grade 4 haematotoxicities in 16.4%, mainly thrombocytopenia. Neurotoxicity occurred in 14.5% of patients and was manageable (grades 1 and 2). 13 patients (24%) stopped the trial treatment during the combination due to progression (6 patients), refusal (3), toxicity (2), AE and delays (1 each). 42 patients (76%) stopped the trial therapy during maintenance due to progression (15), delays (3), non-protocol therapies (2), stem cell transplantation, toxicity and refusal (1 each); the remaining 19 patients (35%) were still under ibrutinib maintenance when the study had to be stopped due to financial issues at the sponsor (SAKK). A detailed overview on side-effects is provided in Fig. 2, and as Supplemental information.

Efficacy of ibrutinib and bortezomib in relapsed or refractory MCL

The ORR to the combination of ibrutinib and bortezomib was 81.8% (90% CI 71.1, 89.8%, Table 2), and the trial therefore met its primary endpoint (H0 to be rejected, p = 0.005). Importantly, the response was a CR unconfirmed (e.g., in patients with a bone marrow infiltration at study entry in which the bone marrow tap was not repeated at the end of the combination therapy) in 12/55 (21.9%). Given the restricted access to PET-CT at many centres when the trial was planned, the response assessment was based on the conservative CT/MRI according to Cheson 1999.[12] With continued ibrutinib maintenance, the ORR increased to 87.3% (90% CI 77.4, 93.9%) and the number of patients with a CR(u) to 41.8%, respectively. Further details of the efficacy analysis, the primary endpoint of phase 2, are provided in Table 2. The median time to best response was 2.4 months (95% CI 2.1, 4.0). The median number of combination cycles was 6 (range 1–6), and 62% of patients received ≥ than 4 cycles. The median duration of the ibrutinib maintenance was 10.6 months (range 1–54 months, Supplemental information).

With a median follow-up of 25.4 months (95% CI 22.4, 31.9), the median duration of objective response was 22.7 months (95% CI 12.3, NA), and the median PFS reached 18.6 months (95% CI 12.5, NA) (Fig. 3). The median OS has not been reached (NR, 36.1; NR). The median duration of response was 30.8 months (95% CI 7.43, NA) in patients with CR/CRu compared with 22.7 months (95% CI 7.95, NA) in PR patients (Fig. 4a). The median PFS was 32.9 months (95% CI 9.33, NA) for CR/CRu patients compared with 24.5 months (95% CI 9.92, NA) in patients with a PR as the best response.

Translational analysis: efficacy of ibrutinib and bortezomib in MCL with high risk features

Given the recent interest in the high-risk features of MCL,[14] the endpoints were also analysed regarding their presence in our patient cohort. This information is

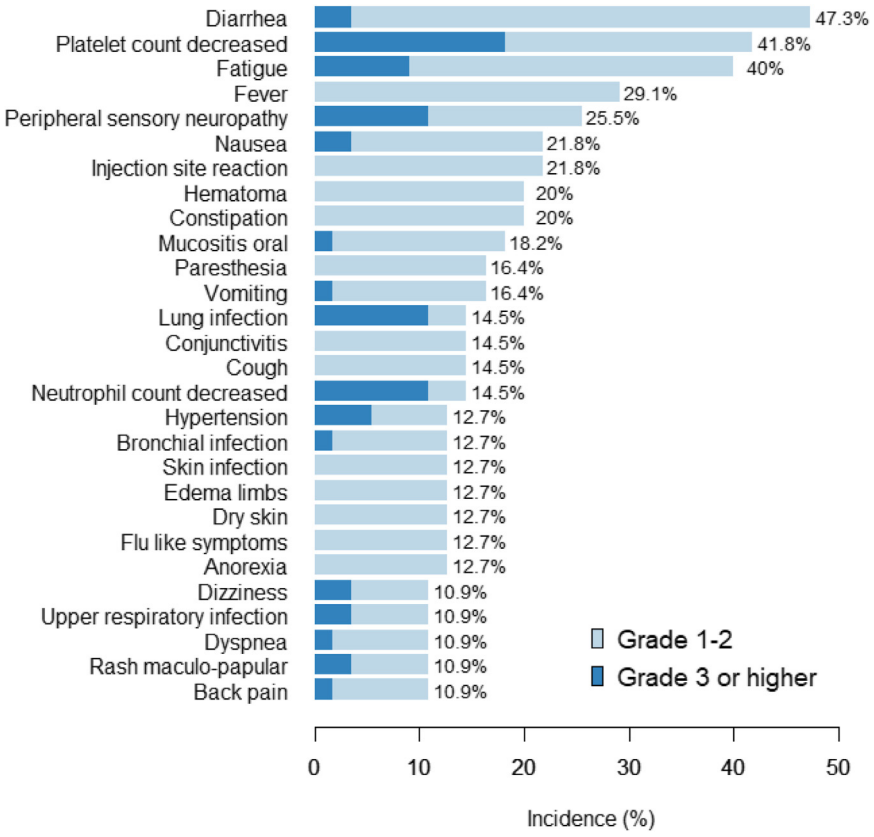

***Fig. 2:* Adverse effects of ibrutinib and bortezomib combination in relapsed or refractory MCL.** Tornado plot showing the incidence of the most common adverse events (>10%), during the whole trial and for the overall population (n = 55). Grade 1–2 adverse events are separated by color.

available in 45/55 (81.8%) of the study population. 34/45 patients (75.6%) had at least one high-risk feature (Ki-67 index >30%, blastoid or pleomorphic variants, p53 overexpression by immunohistochemistry, TP53 mutations and/or deletions). Information on the p53 status was available in a total of 39 patients. Here, we found a 91.7% agreement between the determination of the p53 status by immunohistochemistry and sequencing analysis (Table S4), which is higher than previously reported.[15] Interestingly, the combination of ibrutinib and bortezomib achieved a meaningful activity in relapsed or refractory MCL with high-risk biological features. With an ORR of 74% after the combined induction that increased to 82% during maintenance (Table 3), we found a significant activity of the combination of ibrutinib and bortezomib in these high-risk patients. The time to best response was 2.1 months in the low risk, and 2.4 months in the high-risk group (Table S1). The high-risk population includes a spectrum of known adverse biological features. Albeit based on rather small numbers, the patients with MCL who have blastoid or pleomorphic histologies appeared to profit clearly less from the combination than patients with MCL who had p53 aberrations or any other high-risk feature: the median PFS was only 4.7 months in patients with the blastoid and pleomorphic variants vs. 12 months in patients with p53 aberrations, and 15 months when any high-risk feature was present (Table 3, and Fig. 4c and d).

Combination	No. (%)	Maintenance	No. (%)
Best response		Best response	
n	55		55
CR	9 (16.4%)	CR	19 (34.5%)
CRu	3 (5.5%)	CRu	4 (7.3%)
PR	33 (60.0%)	PR	25 (45.5%)
SD	5 (9.1%)	SD	3 (5.5%)
PD	4 (7.3%)	PD	4 (7.3%)
Not assessed	1 (1.8%)		
Overall response		Overall response	
n	55		
OR	45 (81.8%)	OR	48 (87.3%)

Reported separately at the end of the combination therapy with bortezomib and ibrutinib (left), and during the maintenance with ibrutinib (maintenance, right). CR, complete remission; CRu, complete remission unconfirmed; PR, partial remission; SD, stable disease; PD, progressive disease. Response according to Cheson, 1999.[12]

***Table 2:* Efficacy analysis (primary endpoint).**

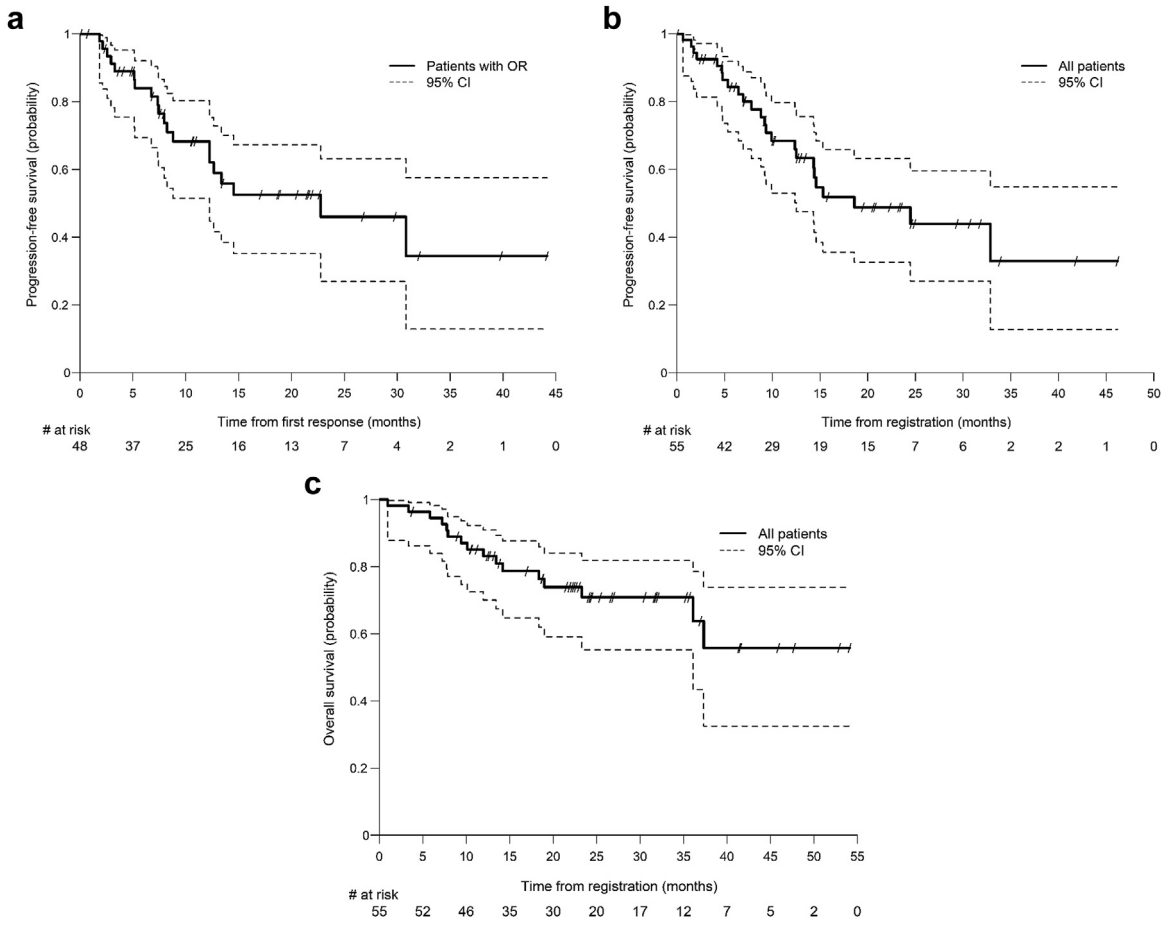

Fig. 3: **Secondary endpoints (whole population)**. **a) Duration of objective response (in the 48 patients with a response)**. Median 22.7 months (95% CI 12.3, NA). **b) Progression-free survival**. Median PFS 18.6 months (95% CI 12.5, NA); PFS, progression-free survival. **c) Overall survival**. The median OS has not been reached; OS, overall survival.

Discussion

After treatment, most patients with MCL will eventually experience a systemic relapse. In this investigator-initiated phase 1/2 trial, we combined ibrutinib and bortezomib to salvage such patients. The two very well-established drugs have non-overlapping toxicities, as well as regulatory approval in relapsed or refractory MCL. The combination of ibrutinib and bortezomib had manageable toxicities consistent with the known safety profiles of the individual drugs. Compared with ibrutinib monotherapy, this includes the exquisite grade 1 and grade 2 neurotoxicity in 14.5% of patients treated with the combination in this trial. Grade 3 infections under ibrutinib monotherapy occur in 11.5%,[16] and in combination with bortezomib in this trial in 25% (mainly pulmonary), whereas treatment discontinuation due to AE in this trial was 9.1%, and 10.3% for ibrutinib in a pooled analysis with a 3.5-year follow up.[3]

At the end of the combination therapy with ibrutinib and bortezomib, we found a clinically significant overall response rate of 81.8%. The response increased to 87.3% with a CR(u) rate of 41.8% upon maintenance with ibrutinib. With a median follow-up of 25.4 months, a median duration of response 22.7 months, and a median PFS of 18.6 months, and reached 30.8 months and 32.9 months, respectively, in patients that achieved a CR/CRu upon the combined induction therapy. The current standard of care with ibrutinib monotherapy achieves an ORR/CR rate of 69.7 and 27.6% respectively, and a median PFS of 12.5 months.[3,4] Several other regimens and combinations, and recently also CAR-T cells and bispecific antibodies, have demonstrated significant clinical activity to treat patients with relapsed or refractory MCL.[1] Relevant for the combination tested here, these new options also include second and third-generation BTK inhibitors such as acalabrutinib,[17] zanubrutinib,[18] and pirtobrutinib,[19] or the combination of ibrutinib and rituximab[20] or venetoclax where three year updated results have been made available.[21–23] In addition, a phase 1/2 trial enrolled patients to assess the

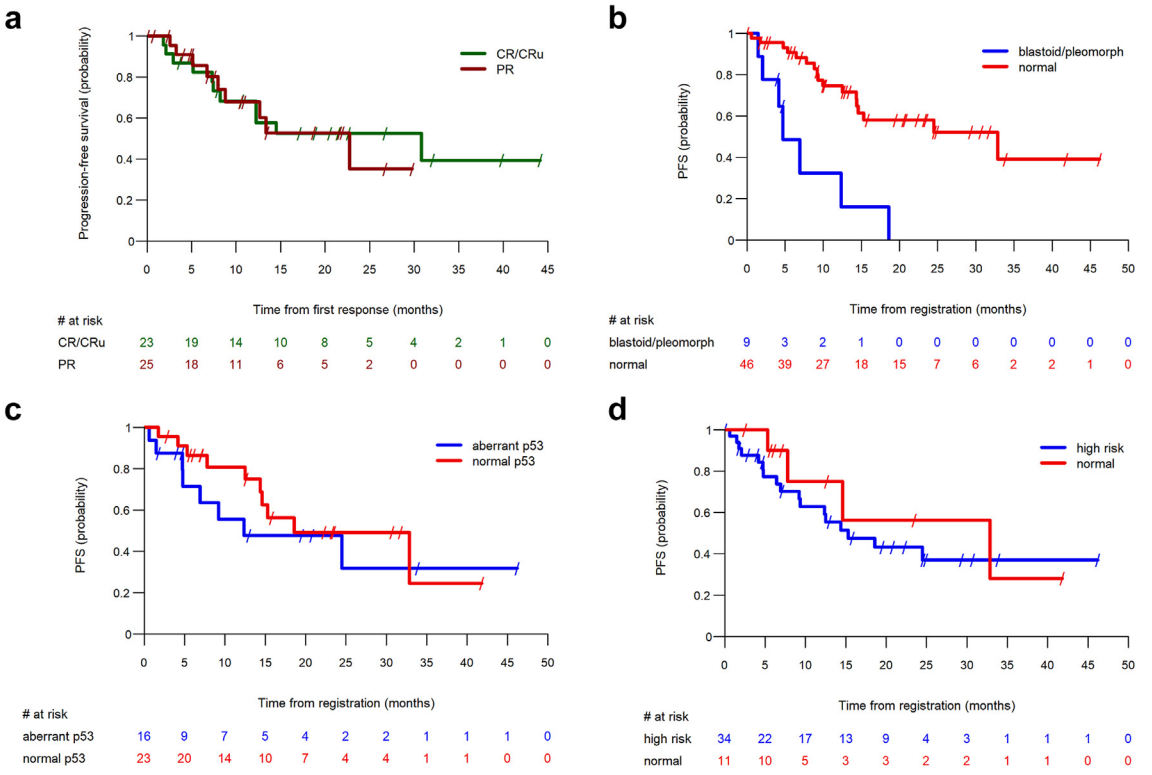

Fig. 4: **Efficacy in subgroups. a) Duration of objective response depending on the response**. Median duration of response in patients with CR/CRu is 30.8 months (95% CI 7.43, NA) vs. 22.7 months (95% CI 7.95, NA) in patients with a PR as best response during the whole trial. CR, complete remission; CRu, complete remission unconfirmed; PR partial remission; CI, confidence interval. **b) PFS in patients with the blastoid/pleomorphic histologic MCL variants**. Median PFS 4.7 (4.2, NA) vs. 33 (15, NA) months. **c) PFS in patients with p53 aberrations**. Median PFS 12 (6.9, NA) vs. 19 (15, NA) months. **d) PFS in patients with any high-risk feature**. Median PFS 15 (9.3, NA) vs. 33 (7.8, NA) months: High-risk features include: Ki-67 index >30%, blastoid or pleomorphic variant, p53 overexpression, TP53 mutations and/or deletions.

combination of ibrutinib with the second-generation proteasome inhibitor ixazomib, but results are not yet available (ClinicalTrials.gov Identifier: NCT03323151). However, in relapsed MCL, with the exception of the RAY trial (ibrutinib vs. temsirolimus, with updated results[24]) informative phase 3 studies that would define a new standard with this level of evidence are currently lacking. The results of the Sympatico trial (ibrutinib ± venetoclax, ClinicalTrials.gov Identifier: NCT03112174) are not yet fully available.[25] In relapsed

Characteristic	N	OR[a]	90% CI (Clopper Pearson)	N	OR[a]	90% CI (Clopper Pearson)
ORR (combination)						
Ki67 (<30 vs. >30)	24	23 (96%)	82%, 100%	28	19 (68%)	51%, 82%
Blastoid/pleomorphic (no vs. yes)	46	40 (87%)	76%, 94%	9	5 (56%)	25%, 83%
Normal vs. aberrant p53 status	23	20 (87%)	70%, 96%	16	13 (81%)	58%, 95%
Any of the above (no vs. yes)	11	10 (91%)	64%, 100%	34	25 (74%)	58%, 85%
ORR (maintenance)						
Ki67 (<30 vs. >30)	24	23 (96%)	82%, 100%	28	22 (79%)	62%, 90%
Blastoid/pleomorphic (no vs. yes)	46	42 (91%)	81%, 97%	9	6 (67%)	34%, 90%
Normal vs. aberrant p53 status	23	22 (96%)	81%, 100%	16	13 (81%)	58%, 95%
Any of the above (no vs. yes)	11	10 (91%)	64%, 100%	34	28 (82%)	68%, 92%

Reported separately at the end of the combination therapy with bortezomib and ibrutinib (above), and during the maintenance with ibrutinib (maintenance, below). ORR, overall response rate; N, number. [a]n (%); CI, confidence interval.

Table 3: **Efficacy analysis by biological risk groups.**

MCL, the addition of bortezomib to high-dose cytarabine has recently been shown to be highly effective.[26]

Patients with high-risk MCL pose a major clinical challenge to achieve long-term disease control. There is growing interest to understand the impact of MCL biology on treatment outcomes.[9] Reports of earlier, but also of recentlylaunched MCL[23] trials did not systematically include or assess information on high risk features, or were limited to the somewhat subjective blastoid variant or clinical factors such as the number of prior treatment lines. Other important clinical trials on relapsed MCL, e.g., using the combination of ibrutinib and rituximab were run largely in low-risk patients,[20] and the large majority (79%) of the patients in the two zanubrutinib trials had a low to intermediate MIPI risk score.[27] Hence, it was reported that responses to ibrutinib and venetoclax are independent of risk markers such as high LDH, the MIPI score or the number of pretreatment lines.[21,22] However, patients with a high Ki-67 index or the blastoid or pleomorphic MCL variants were less likely to achieve a CR with this combination.[21,22] In our trial population of 55 patients with MCL, we assessed the biological high-risk features. 34 of the 45 patients (75.6%), in which all high-risk features could be determined, had at least one high-risk feature (Ki-67 > 30%, blastoid or pleomorphic variant, p53 overexpression, TP53 mutations and/or deletions). In the pooled analysis on ibrutinib monotherapy, were this information is available in 144/370 (38.9%) patients, 13.9% had mutated TP53.[4] Considering that 20/55 (36.3%) of our patients also had >1 (including high-dose consolidation in 29%, counted as one previous line, and up to 5) prior treatment lines, our trial included a high-risk MCL population, which has to be taken into account for descriptive cross-trial comparisons. The reported ORR upon monotherapy with ibrutinib in the population with mutated TP53 is 55%, and the median PFS is only 4.0 months.[3] Monotherapy with acalabrutinib in the updated analysis with an extended follow-up of 26 months showed that the ORR was consistent across refractory patients and with the blastoid/pleomorphic variant, and the authors suggested that some patients with even poorer prognosis may also benefit from this BTK inhibitor.[17] In our trial, we report an ORR of 74% after the induction with ibrutinib and bortezomib and 82% with ibrutinib maintenance and a median PFS of 15 months (Table 3 and Fig. 4d) in patients with the biological high-risk features previously mentioned. We conducted exploratory analyses in our cohort. These efficacy data revealed differences in this high-risk population, e.g., a poor response of the tested combination in the blastoid population (Fig. 4b). However, the efficacy of ibrutinib and bortezomib in the subgroups with the different p53 alterations (overexpression, mutations and locus deletions) revealed no major differences (see details in Supplemental data, and compiled data in Fig. 4c). For patients with p53 aberrations, the combination of ibrutinib and bortezomib achieves an ORR was 81%, and a median PFS of 12 months. Without an a priori stratification for risk factors and all caveats implied by a small sample size, and compared with patients without biological high-risk features, we think that the efficacy in the high-risk population of our cohort, based on the response and for PFS, appears promising. New combinations such as lenalidomide, venetoclax and rituximab or ibrutinib and bendamustine in the first line[28,29] or ibrutinib and venetoclax in relapsed MCL[21,22] have a relatively low benefit in patients with high-risk MCL. Our data, with all limitations of a study with a non-randomised phase 2 design and the lack of a control arm, are an important contribution to the field to overcome the negative prognostic impact at least partially, notably of p53 alterations as one important high-risk feature of patients with MCL. We can only speculate whether the effect is mediated by in vitro demonstrated synergistic increase of proteasomal inhibition by ibrutinib.[10] In addition, we do not know whether the results of this trial can be extrapolated to all currently available BTKi.

Given the restricted use of PET in the countries and sites when the trial was planned, the protocol used the response assessment by CT and MRI, based on the Cheson 1999 criteria.[12] PET increases the number of patients with CR, and through the enhanced ability to detect the difference in PFS between patients experiencing CR and PR, PET is now routine in both clinical practice and trials.[30] This does not hamper the overall results of our trial, but the reported activities from this trial are conservative. This might also explain the lack of an outcome difference in our cohort (Fig. 4) compared with the data e.g., for ibrutinib monotherapy, where patients who achieve a CR do much better than patients with a partial response.[4]

Since the trial was planned, data on the use and value of ibrutinib as part of the first-line therapy in both the younger (WINDOW-1)[31] and the elderly population are now available (SHINE),[29] and the first data of the TRIANGLE trial were recently reported.[32] Just freshly, in the US, pirtobrutinib has been approved, and ibrutinib has been removed from the marked. In addition, the use of bortezomib instead of vincristine as part of the first-line therapy (VR-CAP vs. R-CHOP) has been shown to improve the overall survival in the LYM-3002 trial.[33] The relapsed patient population in the future will probably differ, as patients pretreated with bortezomib and ibrutinib were excluded from SAKK 36/13.

With this investigator-initiated trial, we provide clinical evidence on the value of a combination of ibrutinib and bortezomib, two well established drugs, in patients with MCL. Collectively, we show that this combination is an active regimen to treat patients with relapsed or refractory MCL. We propose this combination as a new and valid option especially for patients with MCL who have biological high-risk features, and as

a comparator for future phase 3 trials incorporating appropriate biomarkers.

Contributors

U.N., E.Z., C.D. and C.R. designed the study; S.S., B.S., S.G., and K.E. provided administrative support; U.N., M.F., M.D., C.S., E.D., T.Z., G.H., U.M., S.F., N.M., C.B., S.B., M.V., A.C., E.Z., C.D., and C.R. provided study materials or patients; V.S.I, T.M., and S.D. did the central pathology review, and performed the determination of the p53 status. U.N. verified the underlying data, S.S. performed the data analysis, and all authors were involved in the interpretation. The manuscript was written by U.N., and all authors have read and approved the manuscript. All authors are accountable for all aspects of the work.

Data sharing statement

Data collected for the study, including individual deidentified participant data and a data dictionary defining each field in the set, can be requested by email to the corresponding author.

Declaration of interests

U.N. reports consulting fees and advisory board participation to/through the institution from and with Janssen-Cilag, Celgene (BMS), Takeda, AstraZeneca, Roche, Novartis, Incyte, Beigene, Kyowa Kirin, Gilead, Pierre Fabre and Miltenyi, payment of honoraria to the institution form Celgene (BMS), Novartis, Takeda, and Gilead, and meeting and/or travel support to the institution from Janssen, Roche, Gilead and Takeda. M.D. reports grants or contracts for research from Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, and Roche to the institution, payment of honoraria from AstraZeneca, Beigene, Gilead/Kite, Janssen, Lilly, Novartis and Roche, meeting and/or travel support from Janssen and Roche, and Data Safety Monitoring Board or Advisory Boards with Abbvie, AstraZeneca, Beigene, BMS/Celgene, Gilead/Kite, Janssen, Lilly/Loxo, Novartis, and Roche. C.S. reports consulting fees from BMS and Janssen, payments of honoraria from BMS and AstraZeneca, and meeting and/or travel support from Kite Gilead. E.D. reports and research funding from ADC Therapeutics and Takeda, consulting fees from Roche, Beigene, Abbvie, AstraZeneca, and Takeda, payments or honoraria from Abbvie, Roche, Incyte and Beigene, support for meetings and/or travel from Abbvie and Beigene, a Data Safety Monitoring Board or Advisory Board role with Abbvie, Beigene, Takeda, and Roche, and the receipt of equipment, materials, drugs, medical writing, gifts or other services from ADC Therapeutics. T.Z. reports consulting fees from Beigene Switzerland GmbH. G.H. reports grants or contracts for research from Gilead/Kite, Incyte, Janssen, Morphosys, Pfizer, Roche, and Abbvie, consulting fees from Abbvie, ADC Therapeutics, AstraZeneca, BMS, Genmab, Gilead/Kite, Incyte, Janssen, Miltenyi, Novartis, Roche, and Lilly, payments or honoraria from Abbvie, AstraZeneca, Beigene, BMS, Genmab, Gilead, Incyte, Janssen, Lilly, and Roche, meeting and/or travel support from Janssen and Gilead/Kite, and Data Safety Monitoring Board or Advisory Boards with Miltenyi. U.M. reports meeting and/or travel support from Janssen-Cilag, an advisory board role with Janssen-Cilag, and participation in the committee of the German-Swiss-Austrian guidelines for mantle cell lymphoma. S.F. reports grants or contracts for research, consulting fees, honoraria, meeting and/or travel support, and advisory board activities from and with Janssen. S.B. reports grants or contracts for research from Janssen-Cilag Neuss and Miltenyi Bergisch Gladbach to the institution, honoraria from Roche, Abbvie, Janssen, AstraZeneca, and Sanofi, and a travel support from Janssen. E.Z. reports grants or contracts for research from AstraZeneca, Beigene, Celgene, Incyte, Janssen, and Roche, for research to the institution from Incyte, AstraZeneca, Beigene, Celgene/BMS, Merck/MSD, and Roche, honoraria for an educational event from Abbvie, an advisory board role with Abbvie, AstraZeneca, Beigene, Celgene/BMS, Celltrion Healthcare, Curis, Eli Lilly, Gilead/Kite, Incyte, Ipsen, Janssen, MeiPharma, Miltenyi Biomedicine, Merck/MSD, and Roche, Data Safety Monitoring Board activities with Merck/MSD, and meeting and/or travel support from Abbvie, Gilead/Kite, Janssen, and Roche, and an expert statement for Bristol Myers Squib. C.R. reports consulting fees to the institution from Abbvie, Celgene/BMS, and Roche, honoraria to the institution from Amgen, Janssen, Abbvie, Celgene/BMS, and Takeda, payment for expert testimonies to the institution from Gilead and Janssen, and meeting and/or travel support from Sanofi and Amgen. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102221.

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