COMPARISON OF IBRUTINIB AND IDELALISIB PLUS RITUXIMAB IN REAL-LIFE RELAPSED/RESISTANT CHRONIC LYMPHOCYTIC LEUKEMIA CASES

Running title: Ibrutinib *versus* Idelalisib in real-life CLL cases

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Novelty statements

- The lack of phase III randomized trials leaves the queries on the choice of the most appropriate BCRi for R/R-CLL patients unresolved
- The efficacy of ibrutinib v*ersus* idelalisib plus rituximab in terms of OS was compared in this real–life study.

- The results suggest the superiority of ibrutinib over idelalisib plus rituximab, independently of a series of well-known confounders, although the influence of potential residual confounding factors cannot be completely excluded.
- The retrospective nature of the study design poses some limits to the interpretation, even though the analyses are adjusted for baseline and biological characteristics.
- This information may be of help for the daily clinical practice.

Abstract

Objectives

To compare the capacity of ibrutinib (IB) and idelalisib-rituximab (IDELA-R) of prolonging overall survival (OS) as in CLL patients, previously previously treated with chemotherapy only.

Methods

A real-life cohort of 675 cases has been identified and investigated in the database of the groups participating in the study.

Results

At an unadjusted univariate analysis, a significant death risk reduction was observed favoring IB (IDELA-R *versus* IB HR=0.5, 95%CI=0.36-0.71) although with some limitations due to the non-randomized and retrospective nature of the study and to the lower number of patients in the IDELA-R group (112 cases) related to the current prescribing practice. To overcome the potential problem of confounding by indication, we adjusted the association between the type of therapy and mortality for all variables significantly associated with OS at Cox univariate analysis. Furthermore, those variables, differently distributed between the two-study groups, were introduced into the multivariate Cox model to improve the effectiveness of the analysis. By introducing all these variables into the multiple Cox regression model, we confirmed the protective effect of IB *versus* IDELA-R (HR=0.67, 95%CI=0.45-0.98, P=0.04) independent of potential confounders.

Conclusions

Although our analysis presents some constraints, i.e. the unavailability of additional potential confounders and the retrospective nature of the study, this observation may be of help for the daily clinical practice, particularly in the absence of randomized trials comparing the two schedules.

Introduction

The treatment algorithm for chronic lymphocytic leukemia (CLL) is rapidly developing, with multiple new drugs being recently approved, including B-cell receptor signaling inhibitors (BCRi), i.e. ibrutinib (IB) [1], idelalisib (IDELA) [2], and the BCL-2 inhibitor venetoclax [3]. These novel agents have entered into the CLL therapeutic armamentarium to substitute for or to integrate the conventional chemo-immunotherapy regimens. This is true especially for the patients with adverse cytogenetic or molecular features such as 17p13.1 deletions [del(17p)] and/or *TP53* mutations (*TP53*mut), or in the relapsing/resistant (R/R) CLL setting [4-6]. In connection with this, the National Comprehensive Cancer Network (NCCN) suggests IB over IDELA plus rituximab (IDELA-R) as the preferred option [7], while the European Society of Medical Oncology (ESMO) recommends IB or IDELA-R in the R/R setting [8]. However, the lack of phase III randomized trials, which unquestionably represents the optimal approach to generate clinical evidence, leaves unresolved queries on the most appropriate BCRi choice for R/R-CLL patients. Thus, despite some well-known limitations and susceptibility to bias, real-life evidence [9] is being progressively exploited in order to address the above-mentioned unanswered issue [10, 11].

In order to maximize the information, potentially provided by the real-life evidence, it is important to have an estimate of the value of all of the potential clinical, molecular and cellular risk factors, given that these risk factors bear considerable relevance for a fair comparison between treatment groups, that could not obviously be randomized at the study start. CLL-IPI, the prognostic value of which was proven in patients treated with chemo-immunotherapy [12], suffers from noticeable limitations when BCRi are utilized [13]. Recently, the assessment of the value of potential risk factors for overall survival (OS), i.e. β2-microglobulin, anemia, LDH, last therapy (BALL score), was carried out in a substantial number of R/R CLL patients treated either with chemo-immunotherapy or with new drugs, with satisfactory results [14]. In addition, we have proposed a simple and parsimonious prognostic score [survival risk score (SRS)], which seems to perform better than the BALL score and may be universally valuable in predicting OS for BCRi treated patients [15, 16].

The aim of this study was that of comparing the efficacy for OS of IB *versus* IDELA-R in patients with R/R-CLL in a real-life cohort of 675 patients. All the above-mentioned risk factors were taken into account to have a precise evaluation of the drug efficacy overriding the confounding effects posed by clinical, cellular or molecular heterogeneity.

Materials and methods

Patients

Five hundred and sixty-three cases received IB and 112 cases IDELA-R as salvage therapy outside of clinical trials. Five hundred and forty-one out of 675 derived from a database of an institutional Italian multicenter working group on CLL (Campus CLL). Overall, 21 Italian, 1 Swiss and 1 Israeli center participated this study (see supplementary data). The final combined database, including R/R CLL patients treated with IB or IDELA-R, was established for research purposes. The database contained clinical information such as age, sex, date of diagnosis, Rai and Binet stage, laboratory parameters, biological markers, treatment history, date of last follow-up or death, which were obtained from clinical records at the time of inclusion and updated on an ongoing basis. The present analysis was performed in 675 cases, 630 of them were included in recent papers [15, 16]. Patients who had previously received only chemotherapy were included in this study.

Immunoglobulin gene mutation and FISH.

IGHV mutation analysis and FISH were performed at the reference laboratory of each participating center. The IGHV mutation status was tested on tumor DNA collected at diagnosis and was assessed according to ERIC guidelines [17]. Sequences that differed by more than 2% from their corresponding germ-line sequence were considered mutated [17-19]. FISH analysis was performed on nuclei extracted from fresh or frozen peripheral blood mononuclear cells. The probe used for 17p deletion analysis was LSIp53 (Abbott). At least 200 interphase cells were examined. The presence of 17p deletion abnormality was scored when the percentage of nuclei with the abnormality was above each laboratory's internal cut-off defined as the mean plus 3 standard deviations (SD) of the frequency of normal control cells exhibiting the abnormality [20].

Statistical analysis

Data are expressed as absolute numbers and percentages and between-groups comparisons were performed by Chi Square Test. The effect of study arms on survival was preliminary investigated by Kaplan-Meier analysis and curves were compared by log rank test. On univariate Cox regression analyses tested covariates for all cause mortality included allocation arm (IB versus IDELA-R) as well as age, gender, Binet stage, line(s) of therapy, exposure to new drug, time from last therapy, anemia, β2M and LDH serum levels, IGHV mutational status, TP53

dysfunction evaluated as del(17p). All univariate correlates of mortality as well as all variables, which significantly differed between the two study arms (P<0.1), were jointly introduced into the same multiple Cox regression model. The potential effect modification by each variable on the allocation arm-mortality link was investigated by assessing the effect of IB versus IDELA-R by the standard linear combination method. In Cox models, data were expressed as hazard ratio, 95% CI and P value. All analyses were performed by SPSS for Windows Version 22, Chicago, Illinois, USA & STATA 13 for Windows StataCorp Lakeway Drive, College Station, Texas, USA.

Results

Demographic and baseline characteristics as well as prognostic markers are summarized in Table 1. In the IDELA-R group there was a significantly higher proportion of cases with high-risk features, including older age, lines of previous therapy, abnormal β2-microglobulin or lactate dehydrogenase (LDH) serum levels, while a trend towards a higher rate of cases with time from last therapy ≤24 months was present in the IB group. Consistently, the intermediate- and high-risk categories of the BALL score (14) (accounting for β2-microglobulin, hemoglobin, LDH values and time from initiation of last therapy) were significantly over-represented in the IDELA-R group, while cases with del(17p) were equally distributed between the two groups (Table 1).

One hundred and nineteen patients (21.1%) discontinued the treatment for toxicity, 67 (11.9%) for CLL progression and 26 (4.6%) for Richter transformation in the IB group, while 50 patients (44.6%) discontinued the treatment for toxicity, 16 (14.3%) for CLL progression, and 2 (1.8%) for Richter transformation in the IDELA-R group. The most common toxicities leading to treatment discontinuation were infection (42 cases) and atrial fibrillation (30 cases) for IB cohort and diarrhea (21 cases), infection (15 cases) for IDELA-R cohort. Median duration of treatment was 18 months (range 1-71 months) for IB cohort and 12 months (range 1-54) for IDELA cohort. After a median follow-up of 1.8 years since BCRi start, 143 patients had died [105 (18.7%) and 38 (33.9%) in the IB and in the IDELA-R group, respectively].

An unadjusted analysis of OS (Figure 1) showed that the IB group experienced significantly longer OS than the IDELA-R group (HR IDELA-R *versus* IB 0.5, 95% CI 0.34-0.72, Table 2).

We adjusted the relationship between allocation groups (IB *versus* IDELA-R) and mortality for all variables significantly associated with OS at Cox univariate analysis (Table 2), i.e. all the four parameters enclosed in the BALL score (14) together with Binet stage C, the number

of previous therapies, and del(17p), independently of their different distribution between the two study groups at the study start (Table 1). Furthermore, to increase the efficiency of data adjustment, all variables, associated to outcome at univariate Cox regression analysis (Table 2), were introduced into the multivariate Cox model (Table 3), independently of being different in the two treatment groups at study inception (Table 1). Despite the potential confounders, the protective effect of IB *versus* IDELA-R (HR=0.65, 95% CI 0.44-0.96, P=0.032) was confirmed following the introduction of all these variables as covariates into the multiple Cox regression model (Table 3). Among the other variables, only the number of previous therapies, anemia, high LDH levels and del(17p) remained independent predictors of OS.

Discussion

Because of the absence of randomized studies, directly confronting IB and IDELA-R, it was decided to investigate a real-life cohort of CLL patients in order to compare the relative efficacy of the two treatments. Although useful in the absence of ad hoc randomized studies, investigations of this type are made complicated by several confounders and particular care should be taken to minimize the so-called "confounding by indication effect". In real-life studies, the potential distortion of the comparison by the two arms (i.e. IB and IDELA-R), operated by potential confounders, can be minimized by adjusting for specific and well-known risk factors of OS. Beyond the strategy adopted here, other methods can be selected with the aim of neutralizing the effects of confounders, including the use of instrumental variables (e.g. center policy related to the prescription of a given drug) or the propensity score matching. However, the application of these approaches was hampered by the lack of an adequate sample size in our setting, especially in the IDELA-R group.

After the potential confounding factors were neutralized by the selected adjustments, IB proved superior to IDELA-R. A role on the greater IB efficacy in terms of OS length could also be linked to the lower incidence of drug withdrawal due to toxicity. Nevertheless, our finding is in line with previous observations reported by a network metanalysis comparing IB *versus* IDELA-R in R/R CLL patients [21]. In this metanalysis, the hazard ratio of IB *versus* IDELA-R was 0.25 (95% CI: 0.12-0.54), a figure lower than that found in our real-life series, suggesting that the context (real-life *versus* clinical trials) may play a crucial role in determining the magnitude of the effect of IB *versus* IDELA-R. Furthermore, after stratifying outcomes by first BCRi choice, it has been shown that a large retrospective series of real-life cases, receiving IB as first choice, experienced a significantly longer PFS in the R/R setting [11]. In addition, preliminary results

indicate a longer PFS for acalabrutinib, a more selective BTK inhibitor than IB, *versus* IDELA-R in the ASCEND phase III trial [22]. Finally, our analysis showed as the number of previous therapies, the anemia, high LDH levels and del(17p) remained independent prognostic factors in line with previous reports [1,14], whereas IGHV mutational status did not. These differences are possibly related to the fact that, while IGHV mutational status is just a predictor of potential future progression, anemia and LDH also are indicators of current disease status, i.e. of ongoing disease progression and are thus likely altered in patients at later disease stages. This explanation is consistent with the fact that a number of IGHV mutated patients also can undergo disease progression. The different weight in predicting outcome of IGHV unmutated status and del (17p) in the cohort is consistent with the more powerful predictive characteristics of the latter marker. In conclusion, the analyses of our and of a few other real-life series [11] support the idea that IB could provide some survival advantage compared to another BCRi like IDELA, in association with rituximab, in the R/R-CLL setting. Regrettably, our analysis presents some constraints. Firstly, some concern on the potential for coding errors inherent to any retrospective analysis of claims databases. Furthermore, even though the analyses are adjusted for some characteristics, unmeasured confounding factors may still be present, thereby reducing the statistical power of sub-analyses. Nevertheless, in line with our results, the updated version of ESMO guidelines does not any longer recommend IB and IDELA-R as equal options, but suggest the use IDELA-R merely in patients who are not eligible for any other therapies [23].

However, the therapeutic algorithms are continuously evolving due to the identification/validation of additional prognostic/predictive factors which may drive the therapeutic choice toward different drugs and/or drug combinations perhaps in specific patients [24], as well as to the advent of novel effective drugs showing either improved toxicity profiles and/or efficacy/effectiveness both in first and subsequent lines of therapy [6].

Ultimately, considering the chronic nature of CLL, all the available therapeutic options could be of help over time in the management of the disease.

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Disclosure of Conflicts of Interest: nothing to disclose

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

References

1. O'Brien S, Furman RR, Coutre S, Flinn IW, Burger JA, Blum K, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131(17):1910-9.
2. Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. J Clin Oncol. 2019;37(16):1391-1402.
3. Roberts AW, Ma S, Kipps TJ, Coutre SE, Davids MS, Eichhorst B, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. Blood. 2019;134(2):111-122.
4. Rossi D, Terzi-di-Bergamo L, De Paoli L, Cerri M, Ghilardi G, Chiarenza A, et al. Molecular prediction of durable remission after first-line fludarabine-cyclophosphamide-rituximab in chronic lymphocytic leukemia. Blood. 2015;126(16):1921-4.
5. Gentile M, Shanafelt TD, Reda G, Mauro FR, Zirlik K, Ciolli S, et al. Validation of a biological score to predict response in chronic lymphocytic leukemia patients treated front-line with bendamustine and rituximab. Leukemia. 2018;32(8):1869-73.
6. Hallek M. Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. Am J Hematol. 2019;94(11):1266-87.
7. Wierda WG, Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Andreadis CB, et al. NCCN Guidelines Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2017. J Natl Compr Canc Netw. 2017;15(3):293-311.
8. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al; ESMO Guidelines Committee. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl5:v78-84.
9. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What Is It and What Can It Tell Us?. N Engl J Med. 2016;375(23):2293–2297.

10. Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N, et al. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. Blood. 2016;128(18):2199–2205.
11. Mato AR, Hill BT, Lamanna N, Barr PM, Ujjani CS, Brander DM, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. Ann Oncol. 2017;28(5):1050–6.
12. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016 Jun;17(6):779-790.
13. Soumerai JD, Ni A, Xing G, Huang J, Furman RR, Jones J, Sharman JP, Hallek M, Adewoye AH, Dubowy R, Dreiling L, Zelenetz AD. Evaluation of the CLL-IPI in relapsed and refractory chronic lymphocytic leukemia in idelalisib phase-3 trials. Leuk Lymphoma. 2019 Jun;60(6):1438-1446.
14. Soumerai JD, Ni A, Darif M, Londhe A, Xing G, Mun Y, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. Lancet Haematol. 2019 Jul;6(7):e366-e374.
15. Gentile M, Morabito F, Del Poeta G, et al. Survival risk score for real-life relapsed/refractory chronic lymphocytic leukemia patients receiving ibrutinib. A campus CLL study [published online ahead of print, 2020 Apr 14]. *Leukemia*. 2020;
16. Gentile M, Martino EA, Visentin A, et al. Validation of a survival-risk score (SRS) in relapsed/refractory CLL patients treated with idelalisib-rituximab. *Blood Cancer J*. 2020;10(9):92.
17. Langerak AW, Davi F, Ghia P, Hadzidimitriou A, Murray F, Potter KN, et al. Immunoglobulin sequence analysis and prognostication in CLL: guidelines from the ERIC review board for reliable interpretation of problematic cases. Leukemia. 2011;25(6):979-84.
18. Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood. 1999;94(6):1840-7.
19. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848-54.

20. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.
21. Sorensen S, Wildgust M, Sengupta N, Trambitas C, Diels J, van Sanden S, et al. Indirect Treatment Comparisons of Ibrutinib Versus Physician's Choice and Idelalisib Plus Ofatumumab in Patients With Previously Treated Chronic Lymphocytic Leukemia. Clin Ther. 2017;39(1):178–189.e5.
22. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, et al. Acalabrutinib vs Rituximab Plus Idelalisib (IdR) or Bendamustine (BR) by Investigator Choice in Relapsed/Refractory (RR) Chronic Lymphocytic Leukemia: Phase 3 ASCEND Study. Haematological Oncology 2019; 37, S2: 86-87.
23. Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Oct 19:S0923-7534(20)42469-X. doi: 10.1016/j.annonc.2020.09.019. Epub ahead of print. PMID: 33091559.
24. Tissino E, Benedetti D, Herman SEM, Ten Hacken E, Ahn IE, Chaffee KG, et al. Functional and clinical relevance of VLA-4 (CD49d/CD29) in ibrutinib-treated chronic lymphocytic leukemia. J Exp Med. 2018;215(2):681-697.

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Figure Legend

Figure 1. Overall survival according to therapy arm.

Table 1. Comparison of the main clinical and biological features of cases treated with Ibrutinib (I, n=563) and with Idelalisib-rituximab (IDELA-R, n=112).

		IB cohort n (%)	IDELA-R cohort n (%)	P*
Age, years	<65	175 (31.1)	21 (18.8)	**0.009**
	≥ 65	388 (68.9)	91 (81.3)	
Sex	female	205 (36.4)	37 (33.0)	0.52
	male	358 (63.6)	75 (67.0)	
Binet stage	A	65 (11.5)	7 (6.2)	**0.062**
	B	248 (44.0)	43 (38.4)	
	C	250 (44.5)	62 (55.4)	
Line of therapy**	2^{nd}	228 (40.5)	26 (23.2)	**0.001**
	$>2^{nd}$	335 (59.5)	86 (76.8)	
Time from last therapy	<24 months	227 (40.3)	34 (30.4)	**0.056**
	≥24 months	336 (59.7)	78 (69.6)	
Anemia***	no	330 (58.6)	60 (53.6)	0.34
	yes	233 (41.4)	52 (46.4)	
β2-microglobulin	<5 mg/dL	418 (74.2)	50 (44.6)	**<0.0001**
	≥5 mg/dL	145 (25.8)	62 (55.4)	
LDH	normal	405 (71.9)	69 (61.6)	**0.032**
	abnormal	158 (28.1)	43 (38.4)	
BALL Score****	low risk	371 (65.9)	30 (26.8)	**<0.0001**
	intermediate risk	149 (26.5)	64 (57.1)	
	high risk	43 (7.6)	18 (16.1)	
***IGHV* mutational status (n=667)**	mutated	179 (32)	46 (42.6)	**0.035**
	unmutated	380 (68)	62 (57.4)	
del(17p)	no	403 (71.6)	86 (76.8)	0.29
	yes	160 (28.4)	26 (23.2)	

* significant P values (<0.05) are highlighted in bold; **median number of lines of therapy is 2 (range 1-9) for IB cohort and 3 (range 1-9) for IDELA-R cohort; *** Anemia is Hb<12 g/dL (men) or <11 g/dL (women); **** the risk categories of the BALL score are computed as reported in ref. 14.

Table 2. Univariate Cox regression analyses of all-cause mortality. 0.5, 95% CI 0.34-0.72

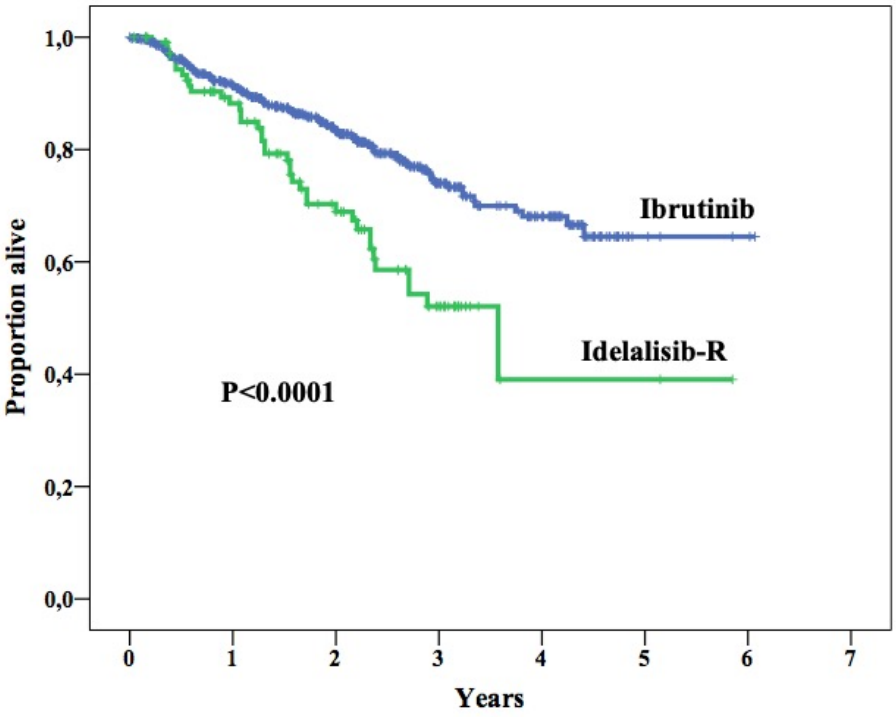
Variables		Hazard Ratio (95% CI)	P*
Therapy	Idela-R	1	
	Ibrutinib	0.5 (0.34-0.72)	**P<0.0001**
Age, years	< 65	1	
	≥ 65	1.42 (0.97-2.1)	P=0.072
Binet stage	A+B	1	
	C	1.64 (1.25-2.16)	**P<0.0001**
Line of therapy	2^{nd}	1	
	$>2^{nd}$	2.33 (1.53-3.55)	**P<0.0001**
Time from last therapy	≥24 months	1	
	<24 months	1.41 (0.98-2.02)	P=0.06
Anemia**	no	1	
	yes	3.47 (2.44-4.93)	**P<0.0001**
β2-microglobulin	<5 mg/dL	1	
	≥5 mg/dL	2.33 (1.67-3.24)	**P<0.0001**
LDH	normal	1	
	elevated	2.76 (1.99-3.83)	**P<0.0001**
IGHV mutational status	mutated	1	
	unmutated	1.1 (0.76-1.56)	P=0.65
del(17p)	no	1	
	yes	1.72 (1.23-2.41)	**P=0.001**

* significant P values (<0.05) are highlighted in bold; **Anemia is Hb<12 g/dL (men) or < 11 g/dL (women)

Table 3. Multivariate Cox regression analyses of all-cause mortality.

Variables		Hazard Ratio (95% CI)	P*
Therapy	Idela-R	1	
	Ibrutinib	0.65 (0.44-0.96)	**P=0.032**
Age, years	< 65	1	
	≥ 65	1.33 (0.89-1.99)	P=0.16
Binet stage	A+B	1	
	C	1.01 (0.76-1.35)	P=0.92
Line of therapy	2^{nd}	1	
	$>2^{nd}$	1.85 (1.20-2.85)	**P=0.005**
Time from last therapy	≥24 months	1	
	<24 months	1.20 (0.80-1.78)	P=0.37
Anemia**	no	1	
	yes	2.70 (1.81-4.02)	**P<0.001**
β2-microglobulin	<5 mg/dL	1	
	≥5 mg/dL	1.18 (0.79-1.76)	P=0.42
LDH	normal	1	
	elevated	1.93 (1.34-2.78)	**P<0.001**
IGHV mutational status	mutated	1	
	unmutated	0.84 (0.582-1.23)	P=0.37
del(17p)	no	1	
	yes	1.70 (1.21-2.40)	**P=0.003**

* significant P values (<0.05) are highlighted in bold; **Anemia is Hb<12 g/dL (men) or < 11 g/dL (women)



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