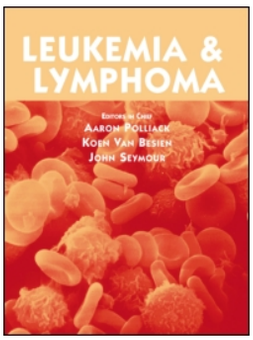

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Exposure–response analysis of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: pooled results from a phase 1b study and the phase 3 MURANO study

Rong Deng, Leonid Gibiansky, Tong Lu, Xiaobin Li, Dan Lu, Chunze Li, Sandhya Girish, Jue Wang, Michelle Boyer, Noopur Shankar, Kathryn Humphrey, Kevin J. Freise, Ahmed Hamed Salem, John F. Seymour, Arnon P. Kater & Dale Miles

To cite this article: Rong Deng, Leonid Gibiansky, Tong Lu, Xiaobin Li, Dan Lu, Chunze Li, Sandhya Girish, Jue Wang, Michelle Boyer, Noopur Shankar, Kathryn Humphrey, Kevin J. Freise, Ahmed Hamed Salem, John F. Seymour, Arnon P. Kater & Dale Miles (2019): Exposure–response analysis of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: pooled results from a phase 1b study and the phase 3 MURANO study, Leukemia & Lymphoma, DOI: 10.1080/10428194.2019.1657575

To link to this article: https://doi.org/10.1080/10428194.2019.1657575

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2019.1657575

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Exposure–response analysis of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: pooled results from a phase 1b study and the phase 3 MURANO study

Rong Deng[a], Leonid Gibiansky[b], Tong Lu[a], Xiaobin Li[a], Dan Lu[a], Chunze Li[a], Sandhya Girish[a], Jue Wang[a], Michelle Boyer[c], Noopur Shankar[a], Kathryn Humphrey[c], Kevin J. Freise[d], Ahmed Hamed Salem[d,e], John F. Seymour[f], Arnon P. Kater[g] and Dale Miles[a]

[a]Genentech Inc, South San Francisco, CA, USA; [b]QuantPharm, LLC, North Potomac, MD, USA; [c]F. Hoffmann – La Roche Ltd, Welwyn Garden City, UK; [d]AbbVie, North Chicago, IL, USA; [e]Department of Clinical Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt; [f]Royal Melbourne Hospital, Peter MacCallum Cancer Centre, & University of Melbourne, Melbourne, Australia; [g]Department of Hematology, Cancer Center Amsterdam, Hovon CLL Study Group, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

ABSTRACT

Exposure–response relationships from a phase 1b (M13-365) and phase 3 (MURANO) study were investigated to assess benefit/risk of venetoclax 400 mg daily plus rituximab in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Dose intensities were summarized by tertiles of predicted venetoclax steady-state average concentrations based on nominal venetoclax dose ($C_{meanSS,nominal}$) for tolerability; exposure–safety analyses used logistic regression. Exposure–progression-free survival (PFS) relationships were assessed using MURANO data, with $C_{meanSS,nominal}$ as a grouping factor. Covariates were demographics, geographic region, study, baseline disease characteristics, ECOG performance status, responsiveness to prior therapy, and chromosomal abnormalities. There was no significant effect of covariates on grade ≥3 neutropenia/infection or PFS, and no relationship between venetoclax exposure and these endpoints, or venetoclax or rituximab dose intensity. These results support the recommended venetoclax 400 mg daily dose in combination with rituximab in patients with R/R CLL or small lymphocytic leukemia.

ARTICLE HISTORY
Received 8 March 2019
Revised 12 July 2019
Accepted 6 August 2019

KEYWORDS
Venetoclax; rituximab; exposure–response analysis; chronic lymphocytic leukemia

Introduction

Venetoclax is an orally administered, highly selective inhibitor of the anti-apoptotic protein BCL-2, which is constitutively overexpressed in chronic lymphocytic leukemia (CLL) [1]. Venetoclax restores apoptosis of cancer cells in a variety of malignancies, including CLL [1]. CLL/small lymphocytic lymphoma (SLL) are the same disease, differing in the predominant location of cancer cells (in blood and bone marrow, and in lymph nodes, respectively) [2,3].

Specific approved indications for venetoclax in the United States include monotherapy or combination with rituximab at a dosage of 400 mg once daily (QD) for the treatment of adult patients with CLL or SLL, and in combination with azacitidine or decitabine or low-dose cytarabine for newly diagnosed acute myeloid leukemia in adults aged ≥75 years [4]. Venetoclax monotherapy dosing (400 mg QD) is supported by exposure–response (ER) analyses [5,6]. Justification for use of the same dose and dose regimen in combination with rituximab was based on pharmacokinetics, tolerability, safety, efficacy, and exposure–safety relationship data obtained from the phase 1b M13-365 [7] and phase 3 MURANO [8] studies, plus exposure–efficacy relationship data from the MURANO study.

Study M13-365 (NCT01682616) was a phase 1b open-label dose-finding study evaluating the safety and tolerability of VenR (venetoclax dosages 200–600 mg QD) in 49 patients with relapsed CLL or SLL which established a recommended phase 2 dose of venetoclax of 400 mg QD for co-administration with rituximab [7].

MURANO (NCT02005471) is an open-label, randomized study investigating the efficacy and safety of venetoclax 400 mg QD in combination with rituximab (VenR) compared with bendamustine plus rituximab (BR) in 389 patients with relapsed/refractory (R/R) CLL

CONTACT Rong Deng deng.rong@gene.com Genentech Research and Early Development, 1 DNA Way, MS463a, South San Francisco, CA 94080, USA

Supplemental data for this article can be accessed here.

[8]. MURANO showed superior progression-free survival (PFS) with VenR over BR, with benefit maintained across clinical and biologic subgroups, including patients with del(17p).

The pharmacokinetics (PK) of venetoclax, and factors affecting exposure to the drug, have been characterized in healthy volunteers and patients with non-Hodgkin lymphoma (NHL), CLL, or SLL, including those with del(17p) [9–14]. The present study was carried out to further evaluate venetoclax ER relationships in patients from the above two key studies, where venetoclax was used in combination with rituximab, to better explore venetoclax 400 mg QD for co-administration with rituximab in R/R CLL or SLL.

Materials and methods

Studies

MURANO [8] enrolled patients with R/R CLL with 1–3 prior lines of therapy, and randomly assigned them to receive VenR ($n = 194$) or BR ($n = 195$). VenR-treated patients received venetoclax over a 5-week dose ramp-up period to reach the target dosage of 400 mg QD, then six cycles of rituximab (single infusion on day 1 of each 28-d cycle) together with ongoing daily dosing of venetoclax. Rituximab was given as a first dose of 375 mg/m^2 (day 1 of cycle 1) followed by 500 mg/m^2 thereafter (cycles 2–6). Patients without disease progression (PD) then continued daily venetoclax therapy until PD or for a maximum of 2 years from cycle 1 day 1. Patients randomized to BR received six cycles (single infusion of rituximab on day 1 and bendamustine infusions on days 1 and 2 of each 28-d cycle) [8]. The data cutoff date for MURANO in this report was 8 May 2017.

Study M13-365 [7] was a phase 1b study in which most patients received an initial dose of venetoclax 20 mg followed by progressive escalation to the designated cohort dose over a 5-week dose ramp-up. After a week at the designated cohort dose, rituximab was added to therapy. Venetoclax was given at target dosages of 200–600 mg QD, with rituximab given monthly (375 mg/m^2 intravenously on day 1, month 1 for most patients, followed by five or seven doses, depending on recruitment relative to a protocol amendment, of 500 mg/m^2 over ~6 months) in patients with relapsed CLL [7]. Of patients enrolled in M13-365, 48 had CLL and one had SLL. Dose cohorts were the following: 200 mg ($n = 6$); 300 mg ($n = 10$); 400 mg ($n = 8$); 500 mg ($n = 7$); 600 mg ($n = 10$); and 400 mg safety expansion ($n = 8$) [7]. Data cutoff in this report was 1 July 2016.

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants.

Determination of venetoclax exposure

Individual venetoclax exposures were estimated using empirical Bayes (*post hoc*) estimates of the primary PK parameters apparent clearance (CL/F) and relative bioavailability (F1) from a population PK model previously described [15]. Individual predicted average steady-state concentrations over the dosing interval were represented using two variables, each of which incorporated patient-specific PK parameters and venetoclax dose as follows: $C_{\text{meanSS,nominal}}$ (individual predicted average steady-state concentration over the dosing interval based on the cohort-assigned [nominal] dose) was calculated as per Equation (1). C_{meanSS} was based on the actual dose at the time of the first treatment-emergent adverse event (AE) during ramp-up and on the cohort-assigned nominal dose thereafter, and calculated as per Equation (2):

$$C_{\text{meanSS, nominal}} = \text{D}_{\text{nom}} * \text{F1}/(\text{CL/F})/\tau \quad (1)$$

and

$$C_{\text{meanSS}} = \text{D} * \text{F1}/(\text{CL/F})/\tau \quad (2)$$

where D_{nom} is the nominal dose assigned to the patient at randomization, D is the dose administered on the day of an event, and τ is the inter-dose interval (1 d). For events noted after the end of the dose ramp-up, D_{nom} was substituted for D in the second equation. Patients without evaluable PK data and not included in the population PK analysis had their primary PK parameters imputed from population estimates and the patient's individual covariate values. Missing continuous covariates were imputed by study using the median value. Missing categorical covariates were imputed by study using the most frequent population value.

Exposure–response relationship analyses

Three sets of analyses were carried out: (1) exposure–dose intensity relationship and (2) exposure–safety relationships (assessed using data from the VenR arm of the MURANO study and the patients from study M13-365) and (3) exposure–efficacy relationships (assessed in patients from the VenR arm of the MURANO study only).

Exposure–dose intensity relationship

In the exposure–dose intensity analysis, venetoclax and rituximab dose intensities in individual patients were grouped and summarized by tertiles of venetoclax $C_{meanSS,nominal}$. Dose intensity was calculated as (total dose received)/(planned total target dose) from the first day of VenR therapy until the last day of actual venetoclax or data cutoff date (whichever came first). Venetoclax and rituximab dose intensities were plotted against venetoclax exposure and examined for correlation.

Exposure–safety relationship

Main exposure–safety analyses were conducted using logistic regression for post-ramp-up treatment-emergent grade $\geq$3 neutropenia or grade $\geq$3 infections, two of the AEs of the greatest interest. Events observed during the dose ramp-up were excluded to avoid confounding of exposure and event times, as patients received weekly escalating venetoclax doses during ramp-up that were lower than the final cohort-assigned dose (i.e. if both an AE and a lower dose are correlated with an earlier time [due to ramp-up period], then there is the potential for the AE and the dose to be correlated with each other through a simple association with time, independent of any causative dose effect). Clinically significant events of neutropenia were identified using the following preferred terms: neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis. Infections, including opportunistic infections, were identified by the system organ class criteria infections and infestations.

Additional exposure–safety analyses (sensitivity analyses) included all events (grade $\geq$3 neutropenia or grade $\geq$3 infections) observed after initiation of venetoclax dosing, including the ramp-up period. Sensitivity analysis 1 evaluated relationships between observed AEs and $C_{meanSS,nominal}$ defined by Equation (1). Sensitivity analysis 2 evaluated the relationships between observed AEs and C_{meanSS} defined by Equation (2). Thus, sensitivity analysis 1 was performed using nominal (cohort-assigned) dose, whereas sensitivity analysis 2 was performed using actual dose (for events observed during ramp-up) or nominal dose (for events observed after the end of ramp-up period) at the time of an AE.

Logistic regression models were implemented to assess correlations between AE probability and venetoclax exposure. The 90% CI around the logistic regression prediction was defined as the 5th and 95th percentiles of model fits to 1000 bootstrap datasets. A significance level of $\alpha = 0.05$ was used to evaluate the exposure coefficient.

A covariate analysis (see below for the tested covariates) was also carried out, in which a forward addition (with $\alpha = 0.01$) – backward elimination ($\alpha = 0.001$) stepwise procedure was implemented. Covariate analysis search procedures performed for the main analysis were not repeated for the sensitivity analyses. The final logistic regression models of the main analyses were applied to the sensitivity analysis datasets.

Exposure–efficacy relationship

Exposure–efficacy relationships were studied using (1) Kaplan–Meier analysis grouped by venetoclax $C_{meanSS,nominal}$ and (2) Cox proportional hazards modeling. Relationships between venetoclax exposure and PFS were first characterized using base Cox models that characterize the marginal effect of venetoclax exposure on PFS without considering covariates. Similar to the AE analysis (above), $\alpha = 0.05$ was used to evaluate the exposure coefficient, and covariate analyses were implemented. The hazard function in the Cox proportional hazards model was expressed as

$$\lambda(t) = \lambda_0(t)\exp(\beta^T\chi)$$

where $\lambda_0(t)$ is the baseline hazard function and χ is a vector of predictor variables, which included continuous exposure ($C_{meanSS,nominal}$) or exposure categories (tertiles of $C_{meanSS,nominal}$) in the base model. The parameter vector β is estimated by maximum partial-likelihood.

Covariate analysis

Covariates tested in the ER analysis included demographics (bodyweight, sex, age, and race), geographic region, study effect (exposure–safety analysis only), and baseline disease characteristics: absolute lymphocyte count, maximum tumor size, number of prior treatment regimens, Eastern Cooperative Oncology Group (ECOG) performance status (PS), responsiveness to prior therapy (exposure–efficacy analysis only), and chromosomal abnormalities (del(17p), del(11q), trisomy 12, del(13q)). There were no covariates with missing data exceeding 15%.

Software

All analyses were performed using the R software, version 3.3.3, for Windows (R project, http://www.r-project.org/). The function *glm()* with logit link was used for the logistic regression analysis. The function

Table 1. Summary of covariates and values at baseline: main exposure–safety analysis population[a].

Continuous covariates	M13-365 ($N = 48$)		MURANO ($N = 191$)		Total ($N = 239$)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Weight (WTKG), kg	76.4 (15.1)	75 (53.8–106.3)	78.7 (14.1)	77 (41–115)	78.2 (14.3)	76.7 (41–115)
Age (AGE), years	67.6 (7.75)	68.5 (50–88)	64 (10.5)	65 (28–83)	64.8 (10.1)	65 (28–88)
Baseline lymphocyte count (BLYMPH), $\times 10^9$/L	54.8 (70.8)	19.6 (0.29–323.5)	75.3 (92.8)	45.7 (0.26–789.5)	71.2 (89.1)	41.4 (0.26–789.5)
Baseline tumor size (BL_TUM), cm^2	37.1 (29.3)	30.4 (0.6–136.7)	61.4 (78.8)	36.7 (2.16–510.5)	56.5 (72.3)	36 (0.6–510.5)
Categorical covariates	M13-365 ($N = 48$) Number (%)		MURANO ($N = 191$) Number (%)		Total ($N = 239$) Number (%)	
No. of patients	48 (100)		191 (100)		239 (100)	
Sex (SEX)						
Male	29 (60.4)		134 (70.2)		163 (68.2)	
Female	19 (39.6)		57 (29.8)		76 (31.8)	
Race (RACE)						
White	47 (97.9)		185 (96.9)		232 (97.1)	
Black	1 (2.1)		–		1 (0.4)	
Asian	–		6 (3.1)		6 (2.5)	
No. of prior treatment regimens						
1	14 (29.2)		109 (57.1)		123 (51.5)	
2	14 (29.2)		57 (29.8)		71 (29.7)	
3	12 (25.0)		21 (11)		33 (13.8)	
4	5 (10.4)		3 (1.6)		8 (3.3)	
5	3 (6.2)		1 (0.5)		4 (1.7)	
ECOG performance status (ECOG)						
0	25 (52.1)		110 (57.6)		135 (56.5)	
1	23 (47.9)		80 (41.9)		103 (43.1)	
2	–		1 (0.5)		1 (0.4)	
Prior idelalisib or ibrutinib therapy						
Not administered	47 (97.9%)		191 (100%)		238 (99.6%)	
Administered	1 (2.1%)		–		1 (0.4%)	
17p deletion (DEL17P)						
No	40 (83.3%)		146 (76.4%)		186 (77.8%)	
Yes	8 (16.7%)		45 (23.6%)		53 (22.2%)	
11q deletion (PQ11)						
No	29 (60.4%)		131 (68.6%)		160 (66.9%)	
Yes	19 (39.6%)		60 (31.4%)		79 (33.1%)	
12q trisomy (PQ12)						
No	36 (75.0%)		168 (88.0%)		204 (85.4%)	
Yes	12 (25.0%)		23 (12.0%)		35 (14.6%)	
13q deletion (PQ13)						
No	25 (52.1)		29 (15.2)		54 (22.6)	
Yes	23 (47.9)		162 (84.8)		185 (77.4)	
Region (REGIONN)						
USA/Canada	32 (66.7)		15 (7.9)		47 (19.7)	
Australia/ New Zealand	16 (33.3)		43 (22.5)		59 (24.7)	
Western Europe	–		65 (34)		65 (27.2)	
Central/ Eastern Europe	–		64 (33.5)		64 (26.8)	
Asia	–		4 (2.1)		4 (1.7)	

[a]Missing continuous covariates were imputed by the median value of the covariate by study. Missing categorical covariates were imputed by the most frequent value in the population by study. There were no covariates with missing data fraction exceeding 15% of study data.
ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

coxph() of the *survival* package was used for Cox proportional hazards modeling.

Results

There were 191 patients from MURANO and 48 from M13-365 in the main exposure–safety analysis; the sensitivity analyses included 194 MURANO and 49 M13-365 patients. Baseline demographics and covariates are shown in Table 1. The last venetoclax treatment day of three VenR patients from MURANO and one from M13-365 was before the end of the ramp-up period. No AE data after the end of the ramp-up period were recorded for these four patients, and they were excluded from the main exposure–safety analysis.

Over two-thirds of patients were male, and the large majority were white (Table 1); race was, therefore, not tested as a covariate. The geographic spread of patients

Table 2. Dose intensity by tertile of venetoclax exposure ($C_{meanSS,nominal}$).

				Dose intensity (%)	
Data source	Drug	Exposure tertile[a]	*N*	Mean (SD)	Median (range)
M13-365 + MURANO	Venetoclax	1	78	91.7 (13.3)	97.2 (48.6–100)
		2	78	89.0 (19.1)	97.8 (26.4–100)
		3	79	88.2 (18.0)	96.3 (16.7–100)
	Rituximab	1	78	101 (6.48)	100 (96.8–157)
		2	76	99.3 (4.68)	100 (65.7–100)
		3	79	99.3 (3.06)	100 (78.3–100)
M13-365	Venetoclax	1	11	93.9 (12.2)	100 (61.6–100)
		2	9	96.0 (10.4)	99.1 (68.4–100)
		3	26	85.9 (21.8)	94.6 (16.7–100)
	Rituximab	1	11	105 (17.3)	100 (96.8–157)
		2	9	97.5 (7.53)	100 (77.4–100)
		3	26	98.1 (5.13)	100 (78.3–100)
MURANO	Venetoclax	1	67	91.3 (13.5)	96.8 (48.6–100)
		2	69	88.0 (19.8)	97.5 (26.4–100)
		3	53	89.4 (15.9)	96.8 (30.7–100)
	Rituximab	1	67	100 (0.03)	100 (99.7–100)
		2	67	99.5 (4.19)	100 (65.7–100)
		3	53	99.9 (0.48)	100 (96.5–100)

[a]Venetoclax $C_{meanSS,nominal}$ exposure tertiles (μg/mL): 1 = 0.322–0.754; 2 = 0.754–1.138; 3 = 1.138–6.481.
$C_{meanSS,nominal}$, venetoclax individual predicted average steady-state concentration over the dosing interval based on the cohort-assigned dose. Tertile bounds were defined for all patients as one group, and then exposure tertile was used as a covariate to summarize data. Bounds were not re-computed for each comparison.
SD: standard deviation.

encompassed USA/Canada (19.7%), Australia/New Zealand (27.2%), Western Europe (27.2%), and Eastern/Central Europe (26.8%). Most patients (81.2%) had one or two prior therapies. Mean and median bodyweight and age were similar for both studies, but lymphocyte counts and tumor burden were higher and more variable in MURANO (Table 1). As only four patients were from Asia, this location was not tested separately as a covariate in exposure–safety logistic regression models. Furthermore, since 103 (43.1%) patients had ECOG-PS 1, and only one had ECOG-PS 2, these two groups were combined for the covariate analysis.

Exposure–dose intensity relationship

The median venetoclax dose intensity in MURANO was ~97% across all tertiles (independent of the venetoclax exposure tertiles). The pooled data showed no apparent differences in venetoclax dose intensity between venetoclax exposure tertiles (Table 2 and Figure 1). Venetoclax dose intensity was only marginally lower in the highest venetoclax exposure group.

The median dose intensity for rituximab was 100% for all venetoclax exposure tertiles for the individual study and pooled data (Table 2 and Figure 1). Venetoclax exposure, therefore, had no effect on rituximab dose intensity.

Exposure–safety relationship

In total, 152 patients (62.6%) had grade ≥3 neutropenia, 123 (50.6%) after the end of the venetoclax dose ramp-up period; 43 (17.7%) had grade ≥3 infection, 36 (14.8%) after dose ramp-up. A histogram of venetoclax steady-state exposure for patients in the exposure–safety relationship analysis is shown in Figure S1A. Logistic regression analyses showed no statistically significant relationship between venetoclax exposure and the probability of developing grade ≥3 neutropenia ($p = 0.136$) or grade ≥3 infections ($p = 0.252$; Figure 2 and Table S1).

Sensitivity analysis 1 (using $C_{meanSS,nominal}$) and sensitivity analysis 2 (using C_{meanSS}) included AE events observed during the ramp-up phase; results from these analyses generally supported the main exposure–safety analysis (Figures S2 and S3 and Tables S2 and S3). In these analyses, the final logistic regression models of the main analysis were applied to the sensitivity analysis datasets. Sensitivity analysis 1 ($p = 0.352$) and sensitivity analysis 2 ($p = 0.147$) both showed no statistically significant association between venetoclax exposure and the probability of grade ≥3 neutropenia. Sensitivity analysis 1 also showed no correlation between venetoclax exposure and the probability of grade ≥3 infection ($p = 0.157$). However, sensitivity analysis 2 showed a decreasing probability of grade ≥3 infection with increasing venetoclax exposure ($p = 0.013$). We note that the logistic regression analysis for sensitivity analysis 2 included events observed during and after the ramp-up period. The actual dose at the time of the event was used to calculate the exposure metric during dose ramp-up, whereas the nominal dose was used in the calculation thereafter. None of the tested covariates, including

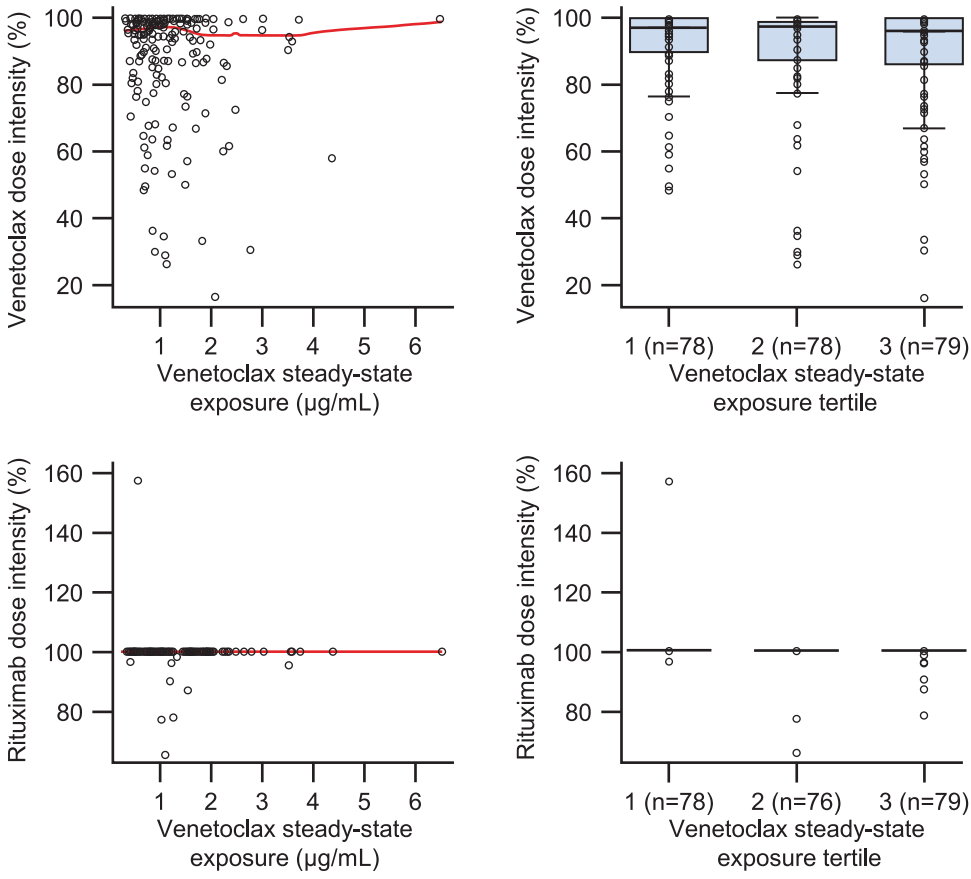

Figure 1. Venetoclax and rituximab dose intensities versus venetoclax exposure (nominal steady-state concentrations over the dosing interval, $C_{meanSS,nominal}$). Pooled data from MURANO and study M13-365. *Left-hand charts*: Circles = individual dose intensity values; red traces = LOWESS trend lines (locally weighted scatterplot smoothing). *Right-hand charts*: Box and whisker plots showing distributions of dose intensity for venetoclax and rituximab. Boxes indicate interquartile ranges (IQRs), with median values indicated by heavy black lines. Whiskers show 1.5 times IQR.

demographics, geographic region, study effect, and baseline disease characteristics, had any significant effect on the probability of grade ≥3 neutropenia or infection.

Exposure–efficacy relationship

Disease progression or death was reported in 32 patients (16.5%) by investigator assessment, and in 35 (18.0%) by independent review committee (IRC). A histogram of venetoclax steady-state exposure for patients in the exposure–efficacy relationship analysis is shown in Figure S1B. Kaplan–Meier plots stratified by tertiles of venetoclax exposure indicated no exposure–PFS relationships in either the investigator or IRC assessment (Figure 3).

In addition, Cox proportional hazard analysis showed that venetoclax exposure is not a significant predictor for PFS (Table 3): 95% CIs of the exposure parameters included zero, indicating that exposure parameters in the models were not significantly different from the null value, and there was no statistically significant relationship between venetoclax exposure and PFS ($p > 0.05$). None of the baseline demographics or disease characteristics tested, including trial stratification factors such as geographic region, CLL risk status, or del(17p) status, significantly affected PFS.

Discussion

Overall, the ER analyses presented here support the recommended dosage of venetoclax 400 mg QD in combination with rituximab for the treatment of patients with R/R CLL.

The analyses showed no significant relationships between venetoclax exposure and grade ≥3 neutropenia or infection or PFS in patients with R/R CLL/SLL receiving VenR from two venetoclax trials, MURANO and M13-365. A weak trend suggesting a negative relationship in venetoclax median dose intensity in study M13-365 (94.6% for high versus 100% for low venetoclax exposure tertiles) was judged not to be clinically relevant. Neutropenia longitudinal modeling could help to further clarify the relationship between

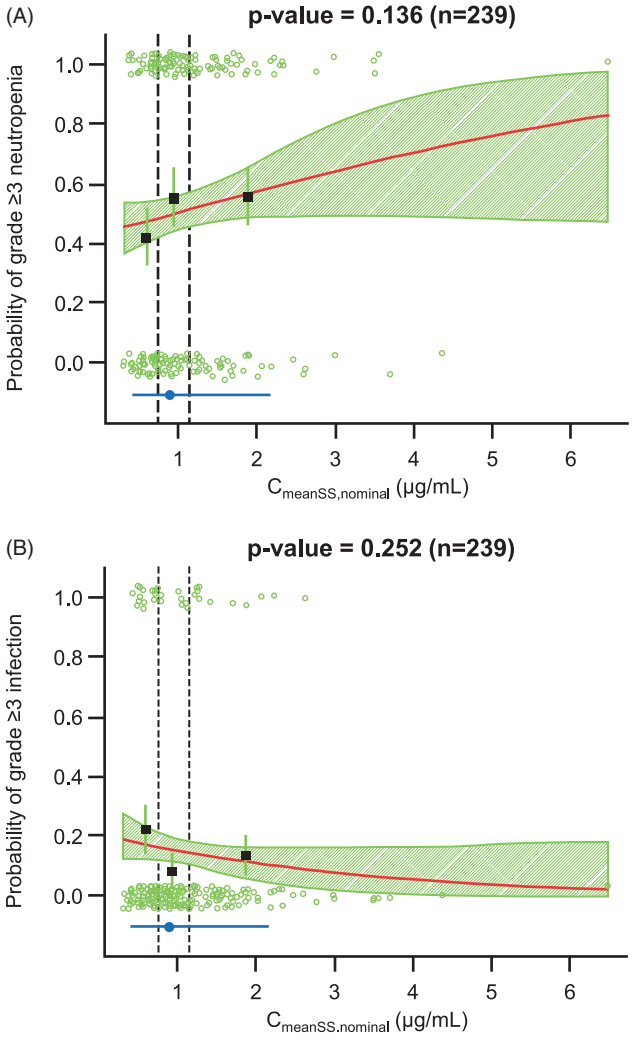

Figure 2. Logistic regression analyses for (A) grade ≥3 neutropenia and (B) grade ≥3 infection. *Notes*: Patients with events (or censoring) after the end of venetoclax ramp-up period were included. $C_{meanSS,nominal}$ was used as a measure of exposure. The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events ($p = 1$) and without events ($p = 0$). Black squares and vertical green lines show observed fraction of patients with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups. Blue point and line: Median and 90% coverage of exposure following 400 mg QD dose of venetoclax.

neutropenia and venetoclax exposure, although this is not currently planned.

Data from MURANO and M13-365 were pooled for the assessment of safety because patients received the same VenR combination were derived from a similar patient population, and had similar safety data collection methods. Adding M13-365 data with multiple dose levels allowed for a wider range of venetoclax exposures than with MURANO alone. However, some differences should be noted in the treatment regimens between studies, including (1) MURANO patients continued venetoclax 400 mg daily until disease progression or for a maximum of 2 years from cycle 1 day 1 (i.e. after completion of the venetoclax ramp-up period), whereas in M13-365 patients were to continue until disease progression, but had the option to stop venetoclax therapy if they had a complete response or if the patient was minimal residual disease-negative; (2) there were small between-study differences in the schedule of rituximab administration. While these differences were not expected to impact ability to pool and analyze safety data, they might confound an evaluation of efficacy endpoints such as PFS. Exposure–efficacy evaluation was, therefore, performed for the MURANO study only.

Co-administration of venetoclax appeared to have no significant effect on the dose intensity of rituximab, patients with higher venetoclax exposures showed similar tolerability of study medication compared with patients with lower exposures, and there was no apparent correlation between venetoclax exposure and the dose intensity of either venetoclax or rituximab in pooled data. There was a small decrease in median venetoclax dose intensity with venetoclax exposure (from 100% in the lowest tertile to 94.6% in the highest tertile) in M13-365, which had a smaller sample size. However, the median venetoclax dose intensity difference across venetoclax exposure tertiles in MURANO was similar (96.8% versus 96.8%). Overall, the results indicated no clinically relevant effect of venetoclax exposure on venetoclax and rituximab dose intensities.

Logistic regression analysis of exposure–safety data from the patients in M13-365 and MURANO showed no statistically significant or clinically relevant associations between venetoclax exposure and the probability of grade ≥3 treatment-emergent neutropenia or infection. The pooled exposure–safety analysis indicated that no significant improvement in safety profiles would be expected with lower venetoclax exposure at the tested lower dosage of 200 mg QD. In addition, graphical and Cox proportional hazards analysis of MURANO patient data showed no statistically significant relationship between venetoclax exposure and PFS. Therefore, there was no evidence to suggest that additional efficacy could be achieved by further increasing venetoclax exposure above what was observed for the studied 400 mg venetoclax QD dose.

For exposure–safety sensitivity analysis 2, safety events observed both during and after the dose

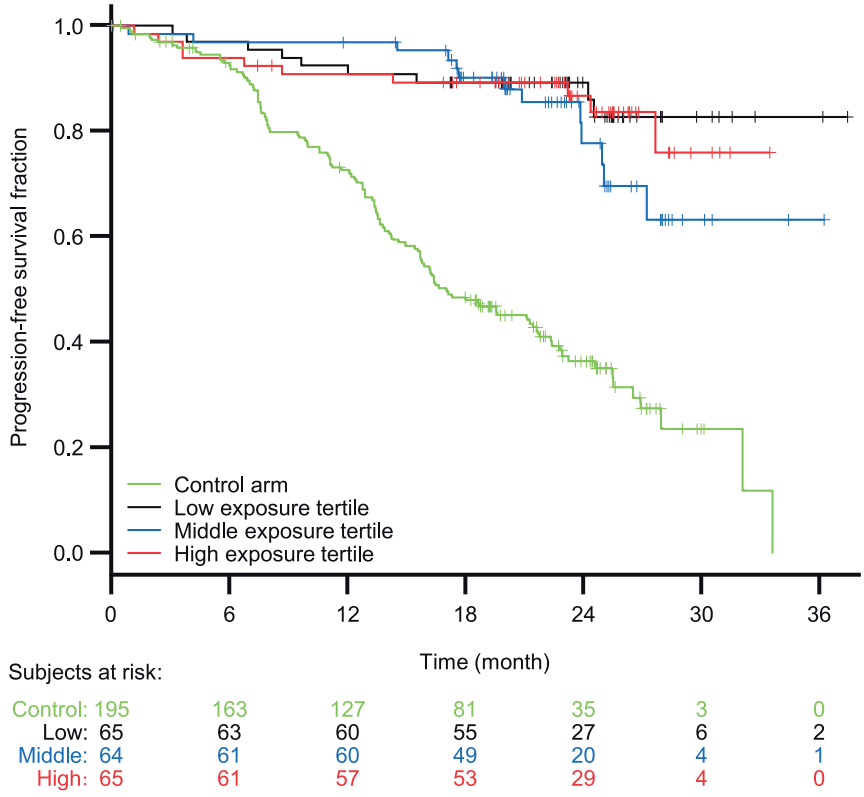

Figure 3. Kaplan–Meier plot of progression-free survival (PFS) by investigator assessment according to venetoclax exposure tertile. PFS by independent review committee assessment yielded similar curves (not shown).

Table 3. Base Cox proportional hazard models for PFS: (a) investigator assessment; (b) independent review committee assessment.

Model	Parameter	β	SE	RSE (%)	HR	95% CI	OF	ΔOF
(a) Investigator assessment								
Base PFS-$C_{meanSS,nominal}$ model	C_{mean}	−0.0410 (mL/μg)	0.329	802.1	0.960	0.504–1.83	310.3	−0.01
Categorical exposure: tertiles of $C_{meanSS,nominal}$	Tertile 2 vs 1	0.454	0.434	95.70	1.57	0.672–3.69	309.0	−1.24
	Tertile 3 vs 1	0.108	0.460	424.4	1.11	0.453–2.74		
(a) IRC assessment								
Base PFS-$C_{meanSS,nominal}$ model	C_{mean}	−0.0608 (mL/μg)	0.320	526.0	0.941	0.503–1.76	310.3	−0.01
Categorical exposure: tertiles of $C_{meanSS,nominal}$	Tertile 2 vs 1	0.239	0.410	171.7	1.27	0.568–2.84	309.0	−1.24
	Tertile 3 vs 1	−0.00954	0.427	4471	0.991	0.429–2.29		

CI: confidence intervals on hazard ratio; $C_{meanSS,nominal}$: venetoclax individual predicted average steady-state concentration over the dosing interval based on the cohort-assigned dose; HR: hazard ratio computed as exp(β); IRC: independent review committee; OF: objective function value; ΔOF: change of the objective function value relative to the null model excluding all parameters; PFS: progression-free survival; RSE: relative standard error of β estimate (%); SE: standard error of β estimate.

ramp-up period were included in the logistic regression analysis, and for the ramp-up period only, the actual dose at the time of the event was used to calculate the steady-state exposure metric used for analysis. This analysis indicated a lower probability of grade ≥3 infections in subjects with higher venetoclax exposure ($p = 0.013$). Because logistic regression analysis does not incorporate the time at which events occur, this finding was likely to be an artifact caused by increased frequency of grade ≥3 infections early in treatment, during the ramp-up period, where lower doses were administered, and the disease burden was higher. Indeed, 10 of 43 patients with grade ≥3 infections had events during ramp-up where actual exposures in sensitivity analysis 2 were lower than nominal exposure (due to lower venetoclax doses in the ramp-up phase). In addition, the association could have been driven by improvement in disease status with treatment, decreasing bone marrow involvement and allowing for expansion of granulocyte progenitors (see Freise et al. [5]). Similar effects over time have been observed with targeted therapy with ibrutinib in CLL/SLL patients [16]. Notwithstanding these observations, there was no statistically significant increase in the probability of grade ≥3 infections with venetoclax exposure in the main analysis when the confounding events from the ramp-up phase were removed.

The present findings were consistent with those from earlier (phases 1–2) pooled R/R CLL and SLL analyses with or without rituximab [5,7,14,17–20]. Venetoclax exposures were estimated using a population PK modeling approach in a manner similar to the present study. However, we used $C_{meanSS,nominal}$ in the main exposure–safety analysis rather than average plasma concentration to the time of the event ($C_{average}$) to avoid bias due to a correlation in time between response and lower exposures due to dose modifications, both of which are more likely the longer a patient is on study. Moreover, $C_{meanSS,nominal}$ isolated the impact of assigned target venetoclax dose and associated steady-state exposure on safety and efficacy, and was not subject to confounding by complex interactions between time and treatment-related or disease-related changes to venetoclax or rituximab dosing. Importantly, the choice of nominal versus actual venetoclax dose as the exposure metric is less likely to confound the interpretation of ER relationships when the venetoclax dose intensity is high, as observed for the VenR combination in this study (97% in the VenR arm of the MURANO study).

One of the objectives of the covariate analysis was to identify patient characteristics that could potentially influence response to venetoclax therapy. As there was no time-dependent component in the current logistic regression analysis, rituximab or granulocyte colony-stimulating factor co-administration was not tested as covariates in the present ER analysis. None of the covariates tested in the present analysis had any significant effects on safety (grade $\geq$3 neutropenia/infection) or efficacy (PFS), including the finding that del(17p) status did not influence the response to venetoclax.

Plasma concentrations of venetoclax in combination with rituximab were comparable with those in previous monotherapy studies [17,18], and co-administration did not lead to clinically relevant changes in the steady-state PK of either agent [15]. Based on prior analysis of observed data, there was little variation in response rates across dose cohorts in M13-365; investigator-assessed ORR ranged from 75% to 100% [7]. Patients who received 400 mg QD of venetoclax ($N = 16$) had the numerically lowest rates of grade 3/4 AEs in the Blood and Lymphatic Disorders System Organ Class (SOC), grade 3/4 pooled AEs for neutropenia, and any AEs across multiple SOCs. Safety and efficacy findings from the phase 3 MURANO study confirmed the clinical benefit of venetoclax at 400 mg QD combined with rituximab in patients with R/R CLL [8].

Conclusions

The ER analysis reported here showed no evidence that higher venetoclax exposure in the MURANO study would result in improved PFS, or that lower venetoclax exposure in the MURANO and M13-365 studies would significantly reduce the probability of developing grade $\geq$3 neutropenia or infections. These ER results are therefore in agreement with earlier findings, and support the recommended dosage of venetoclax 400 mg QD in combination with rituximab for the treatment of patients with R/R CLL or SLL.

Acknowledgments

The authors thank the patients, enrolling physicians, site staff, and venetoclax study teams. The authors also thank Dr Mehrdad Mobasher for his valuable contributions to the manuscript. Third-party medical writing assistance was provided by Christopher Dunn and Andrew Sutton of Gardiner-Caldwell Communications, and was funded by F. Hoffmann – La Roche Ltd.

Disclosure statement

Rong Deng, Tong Lu, Dan Lu, Chunze Li, Sandhya Girish, Jue Wang, Noopur Shankar, and Dale Miles are employees of Genentech and have equity in Genentech/F. Hoffmann-La Roche Ltd. Leonid Gibiansky received consultancy fees from Genentech. Xiaobin Li is an employee of Genentech. Michelle Boyer is an employee of F. Hoffmann-La Roche Ltd and has equity in the company. Kathryn Humphrey is an employee of F. Hoffmann-La Roche Ltd. Kevin J. Freise and Ahmed Hamed Salem are employees of AbbVie and have equity in the company. John F. Seymour received grants from AbbVie, Celgene, Janssen, and F. Hoffmann-La Roche Ltd; consultancy fees from AbbVie, Acerta, Celgene, Janssen, F. Hoffmann-La Roche Ltd, and Takeda; travel support from AbbVie; advisory board fees from Celgene; lecture/speakers' bureaus fees from AbbVie and F. Hoffmann-La Roche Ltd; and expert testimony fees from F. Hoffmann-La Roche Ltd. Arnon P. Kater received grants from F. Hoffmann-La Roche Ltd, Genentech, and AbbVie; consultancy fees from AbbVie; travel support from F. Hoffmann-La Roche Ltd; and lecture/speakers' bureaus fees from AbbVie.

ORCID

Ahmed Hamed Salem http://orcid.org/0000-0002-9261-1583

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx.

For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

References

[1] Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19:202–208.

[2] National Cancer Institute. 2018. 6 May. NCI Dictionary of Cancer Terms. NCI. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cll-sll. Accessed 2019 2 July.

[3] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–2390.

[4] Highlights of prescribing information. VENCLEXTA™ (venetoclax) tablets, for oral use. Initial US Approval: 2016. Revised: May 2019. North Chicago, IL: Abbvie Inc.

[5] Freise KJ, Jones AK, Eckert D, et al. Impact of venetoclax exposure on clinical efficacy and safety in patients with relapsed or refractory chronic lymphocytic leukemia. Clin Pharmacokinet. 2017;56:515–523.

[6] Parikh A, Gopalakrishnan S, Freise KJ, et al. Exposure–response evaluations of venetoclax efficacy and safety in patients with non-Hodgkin lymphoma. Leuk Lymphoma. 2018;59:871–879.

[7] Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. Lancet Oncol. 2017;18:230–240.

[8] Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378:1107–1120.

[9] Jones AK, Freise KJ, Agarwal SK, et al. Clinical predictors of venetoclax pharmacokinetics in chronic lymphocytic leukemia and non-Hodgkin's lymphoma patients: a pooled population pharmacokinetic analysis. AAPS J. 2016;18:1192–1202.

[10] Agarwal SK, Hu B, Chien D, et al. Evaluation of rifampin's transporter inhibitory and CYP3a inductive effects on the pharmacokinetics of venetoclax, a BLC-2 inhibitor: results of a single- and multiple-dose study. J Clin Pharmacol. 2016;56:1335–1343.

[11] Salem AH, Agarwal SK, Dunbar M, et al. Effect of low- and high-fat meals on the pharmacokinetics of venetoclax, a selective first-in-class BCL-2 inhibitor. J Clin Pharmacol. 2016;56:1355–1361.

[12] Freise KJ, Shebley M, Salem AH. Quantitative prediction of the effect of CYP3A inhibitors and inducers on venetoclax pharmacokinetics using a physiologically based pharmacokinetic model. J Clin Pharmacol. 2017;57:796–804.

[13] Agarwal SK, Salem AH, Danilov AV, et al. Effect of ketoconazole, a strong CYP3A inhibitor, on the pharmacokinetics of venetoclax, a BCL-2 inhibitor, in patients with non-Hodgkin lymphoma. Br J Clin Pharmacol. 2017;83:846–854.

[14] Freise KJ, Jones AK, Menon RM, et al. Relationship between venetoclax exposure, rituximab coadministration, and progression-free survival in patients with relapsed or refractory chronic lymphocytic leukemia: demonstration of synergy. Hematol Oncol. 2017;35:679–684.

[15] Deng R, Gibiansky L, et al. Bayesian population model of the pharmacokinetics of venetoclax in combination with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia: results from the Phase 3 MURANO study. Clin Pharmacokinet. 2019. DOI: 10.1007/s40262-019-00788-8

[16] Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015;125:2497–2506.

[17] Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17:768–778.

[18] Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311–322.

[19] Ma S, Brander DM, Seymour JF, et al. Deep and durable responses following venetoclax (ABT-199/GDC-0199) combined with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia: results from a phase 1b study. Blood. 2015;126:830.

[20] Jones J, Mato AR, Coutre S, et al. Preliminary results of a phase 2, open-label study of venetoclax (ABT-199/GDC-0199) monotherapy in patients with chronic lymphocytic leukemia relapsed after or refractory to ibrutinib or idelalisib therapy. Blood. 2015;126:715.