SUPPLEMENTARY APPENDIX

The impact of early discontinuation/dose modification of venetoclax on outcomes in patients with relapsed/refractory chronic lymphocytic leukemia: *post-hoc* analyses from the phase III MURANO study

Anthony R. Mato,[1] Jeff P. Sharman,[2] Juliana M.L. Biondo,[3] Mei Wu,[3] Yong Mun,[3] Su Y. Kim,[4] Kathryn Humphrey,[5] Michelle Boyer,[5] Qian Zhu[3] and John F. Seymour[6]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA/US Oncology Research, US Oncology Network, The Woodlands, TX, USA; [3]Genentech, Inc., South San Francisco, CA, USA; [4]AbbVie, North Chicago, IL, USA; [5]Roche Products Limited, Welwyn Garden City, UK and [6]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, The University of Melbourne, Melbourne, Victoria, Australia

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Correspondence: *ANTHONY R. MATO* - matoa@mskcc.org

SUPPLEMENTAL MATERIAL

The impact of premature discontinuation and interruption of venetoclax on outcomes in patients with relapsed/refractory chronic lymphocytic leukemia: post-hoc analyses from the phase III MURANO study

Mato A, et al.*

Contents

* Corresponding author at Memorial Sloan Kettering Cancer Center, New York, NY, USA, matoa@mskcc.org.

SUPPLEMENTAL METHODS

Literature search on treatment discontinuations and interruptions in CLL

To assess the impact on discontinuation and interruption of novel agents in chronic lymphocytic leukemia, PubMed, Cochrane Central Register of Controlled Trials and EMBASE were searched (through April 2019 for ibrutinib, venetoclax and idelalisib; and through August 2019 for duvelisib) to find literature on treatment discontinuation and interruptions and outcomes. Searches identified English-language articles published from 2015 to 2019 in peer-reviewed journals and included abstracts for presentations at scientific meetings. The search used subject heading and keyword variations (i.e. with/without hyphen, UK/US spelling) based on the following concepts: first-line (1L), relapsed/refractory (R/R), chronic lymphocytic leukemia (CLL), small-cell lymphocytic leukemia (SLL), ibrutinib, venetoclax, idelalisib, duvelisib, overall survival (OS), progression-free survival (PFS), treatment discontinuation and treatment interruption. Additional publications were identified by conducting a manual congress search (including ASCO, ASH, EHA and ICML abstracts published between January 2016 and May 2019).

The selection criteria for published literature included: patients aged ≥18 years with 1L or R/R CLL, who received oral targeted treatment (ibrutinib, idelalisib, duvelisib or venetoclax), with or without concurrent anti-CD20 monoclonal antibody. All study types (including interventional and real-world studies) were permitted, excluding non-systematic reviews, studies with results reported in languages other than English and studies focused on cost. Studies had to report efficacy outcomes (OS and/or PFS) and information on discontinuations and/or interruptions. Exclusion criteria included non-approved oral agents (which during the search dates encompassed acalabrutinib, [FDA approval for treatment of CLL granted in November 2019]).

The primary objective of the literature review was to evaluate the degree to which treatment discontinuations or interruptions with oral targeted therapies (ibrutinib, idelalisib, duvelisib and venetoclax) may limit long-term benefit.

MURANO data and statistical analysis

Event reporting

Reason for premature discontinuation was recorded; however, specific information for treatment interruption was not captured unless associated with an adverse event. Treatment interruption was derived from the drug administration log; any gaps between doses were considered as interruptions.

Disease risk status

Cox proportional hazards regression models were stratified by risk status (low *versus* high). Low disease risk was defined as relapse more than 12 months after chemotherapy, or 24 months after chemoimmunotherapy. High risk was defined as failure to respond to front-line chemotherapy-containing regimens or relapse within 12 months after chemotherapy or within 24 months after chemoimmunotherapy.

Statistical model adjustments

Each statistical model adjusted for different sets of covariates, therefore missing values for any covariate were excluded as part of the statistical models. As such, patient numbers were specific for each individual model and linked to the covariates adjusted for in the model.

Protocol recommendation for treatment interruption due to hematologic toxicity

Guidelines indicated that treatment should be interrupted in the event of specific hematologic toxicity (as higher neutropenia rates were anticipated for the VenR combination, compared to monotherapy). Upon identification of the first episode of Grade 3/4 neutropenia or Grade 3/4 thrombocytopenia, venetoclax and rituximab (if event occurred during the combination phase [Cycles 1–6]) were withheld until counts recovered to Grade ≤2, when previous doses of venetoclax ± rituximab were resumed. If infection and/or fever occurred with Grade 3/4 neutropenia, therapy was stopped until fever and/or infection resolved (fully treated) and counts recovered to Grade ≤2. Granulocyte-colony stimulating factor (G-CSF) or growth factors were administered for neutropenia as indicated; if the patient was not previously receiving prophylactic G-CSF, then it was administered from the first episode through all subsequent treatment cycles.

In the event of recurrent Grade 3/4 neutropenia with/without fever and infection despite G-CSF, venetoclax and rituximab (if neutropenia occurred during Cycles 1–6) were withheld for ≥7 days. G-CSF or growth factors were administered for neutropenia as indicated. When counts recovered to Grade ≤2 and/or platelets were ≥75 × 10^9/L, venetoclax was resumed at one dose level reduction (**Table S6**), while rituximab was reinitiated at the previous dose.

If a patient presented with Grade 4 thrombocytopenia (platelets <25,000/μL) and/or symptomatic bleeding, venetoclax and rituximab (if event occurred during Cycles 1–6) were withheld until bleeding was resolved. Platelets were transfused at the discretion of the investigator. When platelet level increased to Grade ≤2 without transfusional support for 5 consecutive days, venetoclax and rituximab were restarted at previous doses. For a second episode of severe thrombocytopenia and/or symptomatic bleeding and subsequent episodes of severe thrombocytopenia, venetoclax and rituximab (if event occurred during Cycles 1–6) were stopped until platelet level was Grade ≤2 without transfusional support for 5 consecutive days. Venetoclax was then restarted at one dose level reduction (**Table S6**), while rituximab was restarted at the previous dose. In the event of recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, the medical monitor was consulted regarding continuation on the protocol.

SUPPLEMENTAL RESULTS

Literature search on treatment discontinuations and interruptions in CLL

Of the 1,164 publications identified by the literature search, 24 met the selection criteria. These consisted of three publications for venetoclax (including a total of 606 patients), 15 for ibrutinib (including 3,272 patients), five for idelalisib (including a total of 830 patients) and one for duvelisib.

Of the three venetoclax publications (all real-world studies), one described the effect of discontinuations on outcomes while two discussed the effect of interruptions on outcomes (**Table S1**). For ibrutinib, 10 publications described the effect of discontinuations on outcomes (four interventional and six real-world studies), while seven discussed the effect of interruptions on outcomes (two interventional and five real-world studies; **Table S1**). Four of the idelalisib

publications discussed the effect of discontinuations on outcomes (three interventional studies and one real-world study), while one interventional study described the effect of interruptions on outcomes (**Table S1**). The only publication identified for duvelisib was an interventional study that discussed the effect of treatment interruptions on outcomes (no studies discussing the effect of discontinuation of duvelisib treatment on outcomes met the selection criteria; **Table S1**).

MURANO data

Neutropenia

In total 104 patients had a neutropenia (determined based on coded MedDRA preferred term of Neutropenia within the Blood and lymphatic system disorders system organ class) that was related to venetoclax, while all neutropenia AEs for 16 patients were not related to venetoclax. Immunoglobulin heavy chain gene mutation (mutated vs unmutated) and number of prior regimens (>1 vs 1) were significantly associated with venetoclax related neutropenia (p=0.0044 and p=0.0235, respectively), but there were no significant baseline demographic predictors associated with neutropenia not related to venetoclax (**Table S7**).

Gastrointestinal (GI) toxicity

Seventy-one patients had a GI disorder (determined based on coded MedDRA Gastrointestinal disorders system organ class) that was related to venetoclax; for 52 patients all their GI disorders were not related to venetoclax. Response duration to most recent prior therapy (≥12 moths vs <12 months) and renal impairment status were found to be significantly associated with venetoclax related GI disorder (p=0.0160 and p=0.0493, respectively; *Table S8*). Age (≥65 vs <65) was the only baseline covariate significantly associated to GI disorder not related to venetoclax (p=0.0211; **Table S8**).

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SUPPLEMENTAL TABLES

Table S1. Results from the literature search: publications that met the selection criteria.

Targeted treatment	Study type	Publication source)	Study details	Total no. of pts	Type of treatment disruption, n (%)	Outcomes	Conclusion
Ibrutinib	**Interventional**	Jain et al. 2015(1)	Pooled analysis of 4 clinical trials: NCT01105247, NCT01578707 NCT01752426 (all single-agent) and NCT01520519 (ibrutinib plus rituximab)	127	Discontinuation, 33 (26%)	OS	11 pts discontinued due to AEs, 7 due to PD and 6 due to RT. Median survival for all pts with CLL that discontinued was 3.1 months and did not differ significantly between those who discontinued due to PD *vs* those who discontinued for other reasons.
		Maddocks et al. 2015(2)	Pooled analysis of 4 clinical trials (2 phase I/II studies [1 single-agent and 1 ibrutinib + ofatumumab], a phase II study [single-agent] and the RESONATE phase III study [single-agent])*	308	Discontinuation, 76	OS	Pts with PD had a median survival from time of CLL progression of 17.6 months (95% CI 4.7–NR; n=31), while a median OS of only 8 days (95% CI 0–56; n=45) was reported for pts who discontinued for non-relapse reasons. However, this was heavily influenced by pts discontinuing due to infections (n=28). A median OS of 238 days[†] was reported for pts who discontinued due to non-infectious AEs or other reasons (n=17).
		Barr et al. 2017(3)	Ibrutinib arm of the open-label, phase III RESONATE study (single-agent ibrutinib in R/R CLL)	195	Interruption 58[§]	PFS	78 missed-dose events, of which 54 (69%) occurred primarily because of AEs, 10 (13%) because of surgeries, and 3 (0.4%) because of biopsies. Mean duration of a missed-dose event in all treated patients was 18.7 days (range, 8–56). Pts with interruptions for ≥8 consecutive days experienced more IRC-assessed PFS events (17/57 [30%]) than pts missing <8 days (17/137 [12%]), with a significant difference in median PFS (10.9 months *vs* NR; p=0.02).

	Jain et al. 2017(4)	Various clinical trials at M.D. Anderson Cancer Center (between 2010 and 2015)‡	320	Discontinuation, 90	OS	Reason for discontinuing ibrutinib affected median survival of pts: 33 months for intolerance/toxicity (n=29, 32%) *vs* 11 months for miscellaneous reasons (n=28, 31%) *vs* 16 months for PD (n=19, 21%) *vs* 2.3 months for disease transformation (n=9, 10%). The remaining 5 pts discontinued due to transition to commercial supply. Incidence of PD, intolerance and miscellaneous reasons for discontinuation continued to increase after 48 months ($p<0.01$). Median time to discontinuation differed depending on previous treatment (previously untreated pts: 19 months [5–47]; R/R pts: 14.5 months [1.2–54]).
	O'Brien et al. 2018(5)	Two phase III studies (RESONATE, n=135 and RESONATE-2, n=136 [both single-agent])	271	Discontinuation 82	OS	Reasons for discontinuation depended on whether pts had been previously treated; pts with R/R CLL mainly discontinued due to PD, while 1L pts often discontinued due to AEs. The most common AEs leading to discontinuation for previously untreated and R/R pts were infections (4% and 5%, respectively), malignant, benign, or unspecified neoplasms (2% and 5%, respectively), cardiac disorders (3% and 2%, respectively), nervous system disorders (3% and 1%, respectively) and blood and lymphatic system disorders (1% and 2%, respectively). Number of prior therapies affected median OS following discontinuation in these clinical trials (median OS: NR for no prior therapies after a median of 36 months follow-up [n=30] *vs* 9.3 months for 1–2 prior therapies [n=22] and 8.9 months for ≥3 prior therapies [n=30] both with a median follow-up of 44 months).

	Ahn et al. 2019(6)	Phase II study (NCT01500733; single agent)	84	Interruption 75 (89.3%)[‖]	PFS, OS	There was a wide variation in time from start of ibrutinib to first interruption (2 days to 43 months). The most common reason for treatment interruptions were elective procedures (n=152/332 dose interruption events [45.8%]), AEs (n=70/332 [21.1%]) and non-compliance (n=68/332 [20.5%]). Twenty-eight patients (33.3%) had early treatment interruptions of any duration within 6 months of starting ibrutinib and 43 patients (51.2%) had interruptions within the first year. However, analyses at 6 months and 1 year presented no evidence that clinically indicated ibrutinib dose interruptions compromised outcomes.
Real-world	Sandoval-Sus et al. 2015(7)	Moffit Cancer Center, Total Cancer Care and pharmacy registry	54	Discontinuation, 22 (41%)	OS	7 pts discontinued due to PD, 8 due to toxicity and 7 due to proceeding with HSCT. Most common side effects that lead to ibrutinib discontinuation were: major bleeding events (3), atrial fibrillation (2), Grade 3 constipation (1) and Grade 2 recurrent skin rashes (1). The median duration of ibrutinib therapy was 3.7 (0.9–10.9) months. The median OS for CLL pts with PD after ibrutinib and HSCT was 5.5 and 10.8 months, respectively. In pts who discontinued ibrutinib due to toxicity, the median OS was NR. Four pts developed RT upon progression with median OS of 3 months; 3 had del(17p)/complex karyotype. By univariate analysis, RT was associated with inferior OS.
	Thompson et al. 2016(8)	Outcomes in pts who developed ibrutinib-associated AF	56	Interruption, 22	OS	Pts who interrupted treatment at the time of AF onset had a significantly inferior PFS (median 19 months) *vs* pts who reduced dose without interruption (n=13/56) or those who continued full-dose ibrutinib (n=21/56, median 27 months, p=0.023). A trend toward inferior 3-

						year OS was observed in those who interrupted ibrutinib *vs* those who continued without interruption (62% *vs* 74%, p=0.10).
	Akhtar et al. 2017(9)	Retrospective analysis	70	Discontinuation, 25	OS	Pts who discontinued had a mortality rate of 72% (18/25) with a median OS of 17.8 months (95% CI 7.4–28.2) *vs* NR in pts who remained on therapy (p<0.05). Reasons for discontinuation included PD in 13 (52%; 5 with RT), toxicity in 7 (28%; including AF [n=2], sepsis [n=2], pneumonia [n=1], congestive heart failure [n=1] and fatigue [n=1]), and other reasons in 5 (20%) pts (including terminal cancer [n=2], patient preference, alcoholism and insurance issues). A lower median OS was observed in pts who discontinued due to toxicity (5.9 months, 95% CI 3.9–8) *vs* those with RT (11.5 months, 95% CI 3.1–20) and PD (18.2 months, 95% CI 3.8–32.6), although this was not statistically significant (p= 0.117).
	Follows et al. 2017(10)	Updated UK CLL Forum data	315	Discontinuation, 31 and interruption, 32	OS	There was a 7.7-fold increased risk of death for pts who discontinued treatment (due to any cause) compared with those who did not (18-month OS of 40.6% [range, 22.7–57.8] for pts who discontinued treatment compared with 88.1% [range, 81.6–92.5] for pts with no interruptions >14 days). Interruptions of >14 days in 32/315 patients. Impaired survival over 18 months following treatment was reported for pts with temporary breaks >14 days (18-month OS 63% [range, 41.4–78.5]), *vs* pts with standard dosing and no breaks >14 days (18-month OS 88% [range, 81.6–92.5]). This represents a 3.1-fold increased risk of death for pts with interruptions (temporary breaks >14 days) *vs* pts without interruptions.

	Rhodes et al. 2017(11)	Multicenter, retrospective cohort study	391	Interruptions, 86	PFS	No significant impact of dose interruption on 12-month PFS (90% if interruption ≥8 days [n=86, 22%] *vs* 96% if <8 days; HR 1.48, 95% CI 0.48–4.6; p=0.49).
	Sharman et al. 2017(12)	Retrospective analysis from electronic health records of McKesson Specialty Health	447	Discontinuation, 225¶	OS	103 (23.0%) discontinued due to toxicity, 33 (7.4%) discontinued due to PD, 48 (10.7%) discontinued due to other reasons (adequate response achieved, financial, physician choice, patient choice) and 41 (9.2%) discontinued due to death. Similar survival probabilities between patients discontinuing due to toxicity (n=103) or due to PD (n=33). Median OS was similar between pts discontinuing due to toxicity (12- and 24-month survival probabilities of 88.0% [95% CI 79.8–93.0] and 70.5% [95% CI 57.5–80.2], respectively) and due to PD (12- and 24-month survival of 81.8% [95% CI 63.9–91.4] and 75.3% [95% CI 56.5–86.8], respectively). Pts who continued ibrutinib had a 99.5% (95% CI 96.8–99.9) OS at 24 months.
	Winqvist et al. 2018(13)	Swedish compassionate-use program	95	Interruption, 19	PFS, OS	No impact of treatment interruption on PFS or OS for the 19 pts who had a total of 21 treatment breaks >14 days (median 22 days).
	Hampel et al. 2019(14)	Division of Hematology at Mayo Clinic between 2013 and 2017 (outside the context of a clinical trial)	202	Discontinuation, 52	OS	Reasons for discontinuation included toxicity (29, 56%), CLL progression (9, 17%), RT (8, 15%), second malignancy (3, 6%) and other (3, 6%). After discontinuation median OS was 18.5 months. Median OS of pts who discontinued due to toxicity was 27.8 months *vs* 11.5 months for discontinuation due to PD (CLL progression or RT; p=0.04). There were no statistically significant differences in median OS among pts who discontinued according to reason for progression (CLL progression *vs* RT).

		Williams et al. 2019(15)	Observational study including pts with NHL (n=170) or CLL (n=115) at a single institution (University of Rochester Wilmot Cancer Institute between 2014 and 2016)	159	Discontinuation, 51 and interruption, 10**	PFS, OS	Short median OS after discontinuation due to PD (median OS: 1.7 months; 95% CI 0.3–3.7). Pts stopping therapy for other reasons had longer OS after discontinuation (p<0.01; median NR; 95% CI 9.6–NR) than those stopping for PD. CLL-specific survival after discontinuation was similar, with pts who discontinued due to PD having slightly worse OS than those who stopped for AEs (p=0.097; PD: 1.8 months, 95% CI 0.3–NR; AEs: NE, 95% CI 13.3–NR). OS for the pts who required a dose interruption >1 week was similar to those without treatment interruptions (p=0.577). All pts interrupted treatment due to AEs (including febrile neutropenia, anemia, gastrointestinal bleeding, headache, rash, heart palpitations, a surgical procedure and medication interactions in 1 patient each and pneumonia in 2 patients). PFS in these pts was inferior compared with pts without interruptions (p=0.047).
Venetoclax	**Real-world**	Mato et al. 2017(16)	Pooled analysis from 20 academic and community centers	204	Discontinuation, 72 (35%)	PFS, OS	With a median follow-up of 10 months, median PFS/OS had not been reached. Main reasons for discontinuation included PD (47%), RT (21%) and toxicity (11%, most commonly hematologic). Subset univariate analyses identified pre-venetoclax risk factors for inferior PFS, including prior KI exposure (HR 3.7, 95% CI 1.9–7.5; p<0.001), prior cellular therapy (HR 4.6, 95% CI 2.0–10.7; p<0.001), *TP53* interruption (HR 2.8, 95% CI 1.6–5.2; p<0.001) and complex karyotype (HR 1.9, 95% CI 1.0–3.4; p=0.04). For the subset treated with KI therapy, PFS was not reached (median follow-up 7 months).

		Eyre et al. 2019(17)	Conducted by the UK CLL forum	105	Interruption, 43 (41%)	PFS, OS	Temporary interruption of venetoclax did not appear to result in inferior PFS or discontinuation-free survival.
		Roeker et al. 2019(18)	Study from across the USA and the UK	297	Interruption, 95 (32%)	PFS	Median length [range] of interruption was 7 [1–132] days. Interruption (none *vs* ≥1 interruptions) did not impact PFS (p=0.46). Duration of interruptions (≥8 days *vs* <8 days) did not impact PFS (p=0.80).
Idelalisib	**Interventional**	Barrientos et al. 2015(19)	Phase Ib trial of idelalisib in combination with several agents (n=21) and placebo-controlled phase III studies of idelalisib plus rituximab (n=17)	38	Discontinuation, 32	OS	In the phase Ib trial, 18/21 patients discontinued. For these pts toxicity was the most common reason for discontinuation, followed by PD. In particular, Grade 3/4 diarrhea/colitis (33%, n=7/21) was identified as a common reason for discontinuation. After discontinuation (for any reason), median OS (range) was reported as 64 (0–303) days for the 12/38 pts who died following discontinuation; however, most pts included in the combination trials were heavily pretreated and 39% had a high-risk prognostic marker (including deletion of 11q or 17p).
		Brown et al. 2016(20)	A single-agent study and phase III studies of idelalisib in combination with rituximab or ofatumumab	238	Discontinuation, 159 (56%)	OS	Of the pts that discontinued treatment, 10% (n=10) discontinued due to PD and 46% (n=131) for non-PD reasons (AEs, n=87; death, n=7; study withdrawal, n=21; physician's decision, n=14; other, n=12). OS was similar among pts who discontinued, regardless of reason (median OS of 20.9 months following discontinuation due to AEs *vs* 18.8 months following discontinuation due to PD).
		Thompson et al. 2016(21)	Phase II study of idelalisib plus rituximab	40	Discontinuation, 23	PFS, OS	16 pts discontinued due to AEs. A median PFS of 23.3 (8.5–28.6) months (n=5) was reported for pts discontinuing treatment *vs* NR for the entire cohort. Early treatment termination due to toxicity resulted in a statistically significantly

							higher risk (HR 6.61, 95% CI 1.77–16.15; p<0.001) of developing disease progression relative to that seen in patients receiving continuous therapy.
		Ma et al. 2018(22)	Phase III studies (single-agent [n=125] and idelalisib plus anti-CD20 [n=283])	408	Interruption, 219	PFS, OS	49.6% of indolent non-Hodgkin lymphoma pts and 55.5% of R/R CLL pts interrupted therapy. Pts with interruptions (≥1 day of treatment missed due to an AE) achieved a longer PFS and OS than pts with no interruption. Pts with 0, 1 or ≥2 interruptions showed a median PFS of 13.9 months, 20.9 months and 28.9 months, respectively, and a median OS of 33.6 months, NR, and 47.4 months, respectively. CLL pts without interruptions tended to have a shorter total duration of therapy (median duration of therapy: 10.7 months) than pts with either 1 interruption (19 months) or ≥2 interruptions (18.6 months). To account for differences in duration of treatment across the groups, proportions of actual time off therapy were calculated for each pt. Pts who interrupted with median percentage of time off therapy ≤8%, and >8% had improved PFS and OS *vs* pts who had no interruptions (median PFS 13.9 months, 28.9 months, and 16.2 months and median OS 33.6 months, 47.4 months and NR for no, ≤8%, and >8% time off therapy, respectively). While PFS was longer for pts who interrupted with time off therapy <8% compared with >8%, OS was greater with time off therapy >8%. This suggests that treatment interruptions may extend idelalisib treatment duration in some pts, potentially leading to improved outcomes.
	Real-world	Bange et al. 2017(23)	Multicenter retrospective cohort study	61	Discontinuation, 58	PFS, OS	Time to discontinuation was affected by the reason for discontinuation. When discontinuation was due to toxicity (n=16),

							median time to discontinuation was 5 months (range, 0.5–22) for R/R CLL, *vs* 12.5 months (range, 3–42) in R/R CLL when discontinuation was due to PD. Median PFS was 10 months and median OS was not reached when discontinuation was due to toxicity *vs* a median PFS of 13 months and OS of 48 months when discontinuation was due to PD. PFS was not statistically significantly different when stratified by reason for discontinuation (p=0.24, LR test). Stratifying by discontinuation reason showed a median PFS of 10 months in the group discontinuing due to toxicity and 13 months in those discontinuing due to PD.
Duvelisib	**Interventional**	Flinn et al. 2019(24)	Phase III DUO trial (single-agent)	158	Interruption, 126 (80)	PFS	80% (126/158) of pts interrupted treatment, most commonly because of diarrhea (23%), neutropenia (12%), and pneumonia or colitis (11% each). Response was improved or maintained in pts who had ≥1 dose interruption for >1 week (84% [42/50]) or >2 weeks (82% [31/38]) followed by ≥3 weeks on duvelisib, compared with pts who did not experience treatment interruptions. PFS was similar in pts with and without dose interruptions for >1 week (median PFS: 17.8 *vs* 16.3 months, respectively) or >2 weeks (median PFS: 17.8 *vs* 16.3 months) within the first 3 months.

*The two phase Ib/II trials were NCT01105247 (OSU 10032; PCYC 1102) and NCT01217749 (OSU 10053; PCYC 1109), the phase II study was OSU 11133 and the phase III RESONATE study was NCT01578707 (OSU 12024).

†Described as non-infectious AEs or other reasons, which are not clarified in the literature, and calculated as 7.8 months.

‡Including NCT01105247 (2010-0314), NCT01520519 (2011-0785), NCT01292135 (2011-0142), NCT01744691 (2012-1125), NCT01578707 (2012-0707), NCT01752426 (2012-0086), NCT02007044 (2013-0703).

§One patient did not restart therapy prior to data cut-off.

‖28 patients within 6 months, 43 patients in the first year, 75 after a median follow-up of 5.1 years.

¶103 due to toxicity, 33 due to progression, 48 for other reasons and 41 due to death.
**Interruption lasting >1 week.

1L, first-line; AE, adverse event; AF, atrial fibrillation; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; IRC, independent review committee; KI, kinase inhibitors; LR, Log rank; NE, not estimable; NHL, non-Hodgkin lymphoma; NR, not reached; OS, overall survival; PD, progressive disease; pts, patients; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; RT, Richter's transformation

Table S2. Venetoclax related and non-related AEs leading to discontinuation, dose interruption or dose reduction of venetoclax treatment.

	Venetoclax treatment (n=194)					
	Discontinuation		Interruption		Dose reduction	
	Related AEs	Non-related AEs‡	Related AEs	Non-related AEs	Related AEs	Non-related AEs
Number of patients with ≥1 AE, n (%)	18 (9.3)	16 (8.2)	116 (59.8)	55 (28.4)	25 (12.9)	4 (2.1)
Total number of events, n	21	20	252	92	33	4
Blood and lymphatic system disorders, n (%)						
Total number of patients with ≥1 AE	11 (5.7)	4 (2.1)	92 (47.4)	9 (4.6)	18 (9.3)	1 (0.5)
Total number of events	12	4	170	10	24	1
Neutropenia	6 (3.1)	0	80 (41.2)	6 (3.1)	16 (8.2)	0
Thrombocytopenia	3 (1.5)	2 (1.0)	7 (3.6)	2 (1.0)	0	0
Autoimmune hemolytic anemia*	1 (0.5)	1 (0.5)	2 (1.0)	0	0	0
Anemia	1 (0.5)	0	3 (1.5)	0	0	1 (0.5%)
Febrile neutropenia	1 (0.5)	0	3 (1.5)	0	2 (1.0)	0
Immune thrombocytopenic purpura	0	1 (0.5)	0	0	0	0
Agranulocytosis	0	0	1 (0.5)	0	0	0
Disseminated intravascular coagulation	0	0	1 (0.5)	0	0	0
Lymphadenopathy	0	0	1 (0.5)	0	0	0
Pancytopenia	0	0	1 (0.5)	0	0	0
Iron deficiency anemia	0	0	0	1 (0.5)	0	0
Neoplasms benign, malignant and unspecified,† n (%)						
Total number of patients with ≥1 AE	0	5 (2.6)	0	1 (0.5)	0	0
Total number of events	0	5	0	1	0	0
Colorectal cancer	0	2 (1.0)	0	0	0	0
Metastasis	0	1 (0.5)	0	0	0	0
Metastatic malignant melanoma	0	1 (0.5)	0	1 (0.5)	0	0
Pancreatic carcinoma	0	1 (0.5)	0	0	0	0

General disorders and administration site conditions, n (%)						
Total number of patients with ≥1 AE	1 (0.5)	3 (1.5)	5 (2.6)	3 (1.5)	0	0
Total number of events	1	3	5	3	0	0
Pyrexia	1 (0.5)	0	3 (1.5)	0	0	0
Asthenia	0	1 (0.5)	1 (0.5)	0	0	0
Sudden cardiac death*	0	1 (0.5)	0	0	0	0
Sudden death	0	1 (0.5)	0	0	0	0
Influenza-like illness	0	0	1 (0.5)	0	0	0
Fatigue	0	0	0	2 (1.0)	0	0
Soft tissue inflammation	0	0	0	1 (0.5)	0	0
Infections and infestations, n (%)						
Total number of patients with ≥1 AE	2 (1.0)	2 (1.0)	19 (9.8)	31 (16.0)	0	1 (0.5)
Total number of events	3	2	23	47	0	1
Appendicitis	1 (0.5)	0	0	1 (0.5)	0	0
Lung infection	1 (0.5)	0	1 (0.5)	0	0	0
Peritoneal tuberculosis	1 (0.5)	0	0	0	0	0
Pneumonia*	0	2 (1.0)	4 (2.1)	5 (2.6)	0	0
Upper respiratory tract infection	0	0	3 (1.5)	6 (3.1)	0	1 (0.5)
Influenza	0	0	3 (1.5)	1 (0.5)	0	0
Bronchitis	0	0	2 (1.0)	3 (1.5)	0	0
Campylobacter gastroenteritis	0	0	2 (1.0)	0	0	0
Diverticulitis	0	0	1 (0.5)	0	0	0
Herpes simplex otitis externa	0	0	1 (0.5)	0	0	0
Nasopharyngitis	0	0	1 (0.5)	1 (0.5)	0	0
Ophthalmic herpes zoster	0	0	1 (0.5)	0	0	0
Pneumonia influenza	0	0	1 (0.5)	0	0	0
Pneumonia streptococcal	0	0	1 (0.5)	0	0	0
Pharyngitis	0	0	0	3 (1.5)	0	0
Herpes zoster	0	0	0	2 (1.0)	0	0

Sinusitis	0	0	0	2 (1.0)	0	0
Abscess limb	0	0	0	1 (0.5)	0	0
Cystitis	0	0	0	1 (0.5)	0	0
Ear infection	0	0	0	1 (0.5)	0	0
Erysipelas	0	0	0	1 (0.5)	0	0
Gastroenteritis rotavirus	0	0	0	1 (0.5)	0	0
Haemophilus infection	0	0	0	1 (0.5)	0	0
Meningitis	0	0	0	1 (0.5)	0	0
Parvovirus infection	0	0	0	1 (0.5)	0	0
Peridontitis	0	0	0	1 (0.5)	0	0
Pertussis	0	0	0	1 (0.5)	0	0
Respiratory tract infection fungal	0	0	0	1 (0.5)	0	0
Respiratory tract infection viral	0	0	0	1 (0.5)	0	0
Staphylococcal infection	0	0	0	1 (0.5)	0	0
Tooth abscess	0	0	0	1 (0.5)	0	0
Urinary tract infection	0	0	0	1 (0.5)	0	0
Urinary tract infection pseudomonal	0	0	0	1 (0.5)	0	0
Gastrointestinal disorders, n (%)						
Total number of patients with ≥1 AE	2 (1.0)	1 (0.5)	11 (5.7)	6 (3.1)	3 (1.5)	1 (0.5)
Total number of events	2	1	20	9	3	1
Crohn's disease	1 (0.5)	0	0	0	0	0
Diarrhea	1 (0.5)	0	7 (3.6)	2 (1.0)	2 (1.0)	0
Ascites	0	1 (0.5)	0	0	0	0
Nausea	0	0	6 (3.1)	1 (0.5)	0	0
Abdominal pain	0	0	1 (0.5)	2 (1.0)	0	0
Abdominal pain upper	0	0	1 (0.5)	0	0	0
Vomiting	0	0	1 (0.5)	2 (1.0)	0	0
Gastrointestinal hemorrhage	0	0	0	1 (0.5)	0	0
Inguinal hernia	0	0	0	1 (0.5)	0	0
Abdominal discomfort	0	0	0	0	1 (0.5)	0

Small intestinal obstruction	0	0	0	0	0	1 (0.5)
Investigations, n (%)						
Total number of patients with ≥1 AE	2 (1.0)	0	12 (6.2)	3 (1.5)	2 (1.0)	0
Total number of events	2	0	21	4	3	0
Alanine aminotransferase increased	1 (0.5)	0	3 (1.5)	0	1 (0.5)	0
Neutrophil count decreased	1 (0.5)	0	5 (2.6)	0	1 (0.5)	0
Aspartate aminotransferase increased	0	0	2 (1.0)	0	1 (0.5)	0
Blood bilirubin increased	0	0	1 (0.5)	1 (0.5)	0	0
Blood creatinine increased	0	0	1 (0.5)	0	0	0
Gamma-glutamyltransferase increased	0	0	1 (0.5)	0	0	0
Serum ferritin increased	0	0	1 (0.5)	0	0	0
Blood alkaline phosphatase increased	0	0	0	1 (0.5)	0	0
Blood lactate dehydrogenase increased	0	0	0	1 (0.5)	0	0
Respiratory, thoracic and mediastinal disorders, n (%)						
Total number of patients with ≥1 AE	0	2 (1.0)	0	2 (1.0)	0	0
Total number of events	0	2	0	2	0	0
Acute respiratory failure	0	1 (0.5)	0	0	0	0
Hydrothorax	0	1 (0.5)	0	0	0	0
Productive cough	0	0	0	1 (0.5)	0	0
Pulmonary embolism	0	0	0	1 (0.5)	0	0
Ear and labyrinth disorders, n (%)						
Total number of patients with ≥1 AE	1 (0.5)	0	0	0	0	0
Total number of events	1	0	0	0	0	0
Vertigo	1 (0.5)	0	0	0	0	0
Nervous system disorders, n (%)						
Total number of patients with ≥1 AE	0	1 (0.5)	0	2 (1.0)	0	0
Total number of events	0	1	0	2	0	0
Status epilepticus	0	1 (0.5)	0	0	0	0

Dizziness	0	0	0	1 (0.5)	0	0
Lacunar infarction	0	0	0	1 (0.5)	0	0
Metabolism and nutrition disorders, n (%)						
Total number of patients with ≥1 AE	0	0	6 (3.1)	4 (2.1)	1 (0.5)	0
Total number of events	0	0	6	5	2	0
Tumor lysis syndrome	0	0	4 (2.1)	0	0	0
Hypokalemia	0	0	1 (0.5)	1 (0.5)	1 (0.5)	0
Hyperphosphatemia	0	0	1 (0.5)	0	0	0
Hyponatremia	0	0	0	0	1 (0.5)	0
Decreased appetite	0	0	0	1 (0.5)	0	0
Dehydration	0	0	0	1 (0.5)	0	0
Vitamin B12 deficiency	0	0	0	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders, n (%)						
Total number of patients with ≥1 AE	0	0	2 (1.0)	1 (0.5)	0	0
Total number of events	0	0	2	2	0	0
Myalgia	0	0	1 (0.5)	0	0	0
Polyarthritis	0	0	1 (0.5)	0	0	0
Tenosynovitis	0	0	0	1 (0.5)	0	0
Skin and subcutaneous tissue disorders, n (%)						
Total number of patients with ≥1 AE	0	0	2 (1.0)	1 (0.5)	1 (0.5)	0
Total number of events	0	0	2	1	1	0
Eczema	0	0	2 (1.0)	0	0	0
Alopecia	0	0	0	0	1 (0.5)	0
Transient acantholytic dermatosis	0	0	0	1 (0.5)	0	0
Cardiac disorders, n (%)						
Total number of patients with ≥1 AE	0	0	1 (0.5)	1 (0.5)	0	0
Total number of events	0	0	1	1	0	0
Myocardial infarction	0	0	1 (0.5)	0	0	0
Myocardial ischemia	0	0	0	1 (0.5)	0	0

Hepatobiliary disorders, n (%)						
Total number of patients with ≥1 AE	0	0	1 (0.5)	1 (0.5)	0	1 (0.5)
Total number of events	0	0	1	1	0	1
Hyperbilirubinemia	0	0	1 (0.5)	0	0	0
Bile duct obstruction	0	0	0	1 (0.5)	0	0
Portal vein thrombosis	0	0	0	0	0	1 (0.5)
Vascular disorders, n (%)						
Total number of patients with ≥1 AE	0	0	1 (0.5)	1 (0.5)	0	0
Total number of events	0	0	1	1	0	0
Hypotension	0	0	1 (0.5)	0	0	0
Deep vein thrombosis	0	0	0	1 (0.5)	0	0
Injury, poisoning and procedural complications, n (%)						
Total number of patients with ≥1 AE	0	0	0	2 (1.0)	0	0
Total number of events	0	0	0	2	0	0
Humerus fracture	0	0	0	1 (0.5)	0	0
Ulna fracture	0	0	0	1 (0.5)	0	0
Reproductive system and breast disorders, n (%)						
Total number of patients with ≥1 AE	0	0	0	1 (0.5)	0	0
Total number of events	0	0	0	1	0	0
Uterine hemorrhage	0	0	0	1 (0.5)	0	0

*Includes event for patient whose primary reason for discontinuation was not due to an AE (primary reason for discontinuation for the patient with autoimmune hemolytic anemia was physician decision, for the patient with sudden cardiac death was death and for the patient with pneumonia was physician decision);

†Including cysts and polyps.

‡No coding available for one patient (2 events).

AE, adverse event.

Table S3. Baseline demographic predictors (logistic regression model) for patients who discontinued venetoclax due to AEs.

	Discontinuation due to AEs		Discontinuation due to venetoclax related AEs		Discontinuation due to venetoclax non-related AEs	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (≥65 *vs* <65 years)	0.9 (0.2–3.9)	0.8685	0.7 (0.2–2.9)	0.5798	11.2 (0.5–260.1)	0.1312
Sex (female *vs* male)	0.6 (0.2–2.7)	0.5369	0.7 (0.1–3.1)	0.5983	0.2 (0.0–6.6)	0.3696
Race (white *vs* non-white)	0.8 (0.0–15.2)	0.8797	0.2 (0.0–3.4)	0.2728		
Chromosome 11q deletion (abnormal *vs* normal)	1.2 (0.3–4.9)	0.7576	1.6 (0.4–6.4)	0.4768	0.2 (0.0–3.3)	0.2395
***TP53* mutation** (mutated *vs* unmutated)	1.1 (0.2–5.1)	0.9469	1.0 (0.2–5.5)	0.9938	0.7 (0.0–13.2)	0.8320
IGVH (mutated *vs* unmutated)	2.4 (0.5–10.7)	0.2627	3.3 (0.6–16.4)	0.1532	0.8 (0.0–24.6)	0.8819
Beta-2 microglobulin (>3.5 *vs* ≤3.5 mg/L)	3.0 (0.5–17.4)	0.2101	2.3 (0.4–13.8)	0.3540	2.1 (0.1–65.7)	0.6694
Rai stage		0.3696				
Stage 1 *vs* 0	0.1 (0.0–1.1)					
Stage 2 *vs* 0	0.4 (0.1–2.3)					
Stage 3 *vs* 0	0.2 (0.0–2.0)					
Stage 4 *vs* 0	0.4 (0.1–3.0)					
Bulky disease (≥5 *vs* <5 cm)	1.3 (0.3–6.0)	0.7624	1.0 (0.2–5.2)	0.9617	0.6 (0.0–15.9)	0.7317
Number of prior regimens (>1 *vs* 1)	1.6 (0.5–5.7)	0.4546	1.9 (0.5–7.4)	0.3374	1.0 (0.1–10.0)	0.9718
Response duration to most recent prior therapy (≥12 *vs* <12 months)	0.3 (0.1–1.0)	0.0491	0.4 (0.1–1.9)	0.2760	0.0 (0.0–1.0)	0.0467
Renal impairment status		0.5868		0.4805		0.2167
Mild *vs* normal	0.9 (0.2–3.9)		1.8 (0.3–10.0)		0.0 (0.0–1.5)	
Moderate *vs* normal	2.4 (0.3–21.2)		4.3 (0.4–46.2)		0.5 (0.0–13.6)	

AE, adverse event; CI, confidence interval; IGVH, immunoglobulin heavy chain gene mutation.

Table S4. Baseline demographic predictors (logistic regression model) for patients who interrupted treatment and reduced venetoclax dose due to AEs.

	Interruption due to venetoclax related AEs		**Interruption due to venetoclax non-related AEs**		**Reduction due to venetoclax related AEs**	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (≥65 *vs* <65 years)	0.5 (0.2–1.4)	0.1721	1.2 (0.3–5.1)	0.7901	1.0 (0.2–3.9)	0.9479
Sex (female *vs* male)	2.3 (0.8–6.4)	0.1079	0.2 (0.0–1.7)	0.1317	0.9 (0.3–3.3)	0.9265
Race (white *vs* non-white)	0.2 (0.0–3.3)	0.2552				
Chromosome 11q deletion (abnormal *vs* normal)	0.6 (0.2–1.4)	0.2120	0.7 (0.2–2.8)	0.5616	2.1 (0.6–7.0)	0.2309
***TP53* mutation** (mutated *vs* unmutated)	2.1 (0.6–6.8)	0.2411	2.3 (0.5–11.3)	0.3080	0.8 (0.2–3.7)	0.8140
IGVH (mutated *vs* unmutated)	1.9 (0.7–5.6)	0.2436	1.9 (0.3–11.2)	0.4847	1.4 (0.4–5.4)	0.6254
Beta-2 microglobulin (>3.5 *vs* ≤3.5 mg/L)	1.2 (0.4–3.8)	0.7142	3.1 (0.5–21.1)	0.2416	0.5 (0.1–2.3)	0.4064
Rai stage		0.2888		0.9069		0.7111
Stage 1 *vs* 0	2.9 (0.8–10.4)		0.8 (0.1–5.5)		1.6 (0.3–7.7)	
Stage 2 *vs* 0	4.5 (1.1–18.5)		0.7 (0.1–5.7)		1.0 (0.2–6.2)	
Stage 3 *vs* 0	3.4 (0.6–18.4)		1.0 (0.1–9.5)		1.5 (0.1–20.0)	
Stage 4 *vs* 0	2.7 (0.5–13.8)		0.3 (0.0–3.9)		3.2 (0.5–21.1)	
Bulky disease (≥5 *vs* <5 cm)	1.5 (0.5–4.5)	0.4224	2.3 (0.5–10.9)	0.3132	1.8 (0.5–6.8)	0.4029
Number of prior regimens (>1 *vs* 1)	3.7 (1.5–9.1)	0.0048	0.6 (0.1–2.3)	0.4200	2.1 (0.7–6.6)	0.1966
Response duration to most recent prior therapy (≥12 *vs* <12 months)	1.0 (0.4–2.8)	0.9721	0.7 (0.2–3.2)	0.6795	2.5 (0.7–9.7)	0.1803
Renal impairment status		0.7469				0.1184
Mild *vs* normal	1.2 (0.4–3.3)				1.5 (0.4–5.9)	
Moderate *vs* normal	1.9 (0.4–10.3)				6.6 (1.0–44.9)	
Hepatic impairment status		0.7034		0.8997		0.0933
Mild *vs* normal	0.9 (0.3–2.9)		0.7 (0.1–4.0)		0.3 (0.0–2.3)	

Moderate/severe *vs* normal	2.1 (0.3–12.5)	1.2 (0.1–16.3)	4.4 (0.8–25.2)

AE, adverse event; CI, confidence interval; IGVH, immunoglobulin heavy chain gene mutation.

Table S5. Publications from the literature search that met the selection criteria and discuss dose reduction.

Targeted treatment	Study type	Publication source)	Study details	Total no. of pts reducing treatment	Outcomes	Conclusion
Ibrutinib	**Interventional**	Ahn et al. 2019(6)	Phase II study (NCT01500733; single agent)	12/84*	PFS, OS	After a median follow-up of 39.4 months from the first dose reduction, only 1 patient progressed. In multivariate analysis, dose intensity was associated with PFS or OS. No evidence that clinically indicated that ibrutinib dose reductions compromised long-term outcomes.
	Real-world	Thompson et al. 2016(8)	Outcomes in pts who developed ibrutinib-associated AF	13/56	PFS	Patients who were managed with dose reductions had superior PFS compared with those patients who interrupted ibrutinib at the time of AF onset. This outcome in CLL control is likely related to the low rate of patients (14%) who subsequently successfully restarted ibrutinib after interruptions.
		Follows et al. 2017(10)	Updated UK CLL Forum data	48/315	OS	Of the 48 patients who had dose-reduced ibrutinib without treatment breaks in the first year, 17 stopped the drug, 10 died, 25 continued on dose-reduced ibrutinib and 6 returned to standard dose. There was no statistical difference in OS between standard dosing with no breaks >14 days and dose reductions but no breaks >14 days (88.1% [95% CI 81.6–92.5] vs 83.7% [95% CI 66.8–92.5]; p=0.75).
		Rhodes et al. 2017(11)	Multicenter, retrospective cohort study	30/391 (7.6%)†	PFS	Patients starting at lower doses had inferior PFS. 12-month PFS was 71% for dose reduction *vs* 93% with the full dose (HR 3.3, 95% CI 1.5–7.0; p=0.003).

		Williams et al. 2018(15)	Observational study including pts with NHL (n=170) or CLL (n=115) at a single institution (University of Rochester Wilmot Cancer Institute between 2014 and 2016)	5/159‡	PFS, OS	Patients who required an early dose reduction had a significantly worse PFS (p=0.004) and OS (p=0.014) than those who maintained dosing.
Venetoclax	**Real-world**	Eyre et al. 2019(17)	Conducted by the UK CLL forum	NR	PFS, OS	Dose reduction of venetoclax did not appear to result in inferior PFS or discontinuation-free survival.
		Roeker et al. 2019(18)	Study from the USA and the UK	29%§	PFS	PFS was similar for those whose final venetoclax dose was 400 compared with <400 mg. Dose reductions (8 *vs* <8 days) did not impact PFS.
Duvelisib	**Interventional**	Flinn et al. 2019(24)	Phase III DUO trial (single-agent)	43/158 (27%)		The median time to dose reduction after CR/PR was 5.6 months (n=25) and median duration was 3.4 months. Proportions of patients experiencing AESIs were stable or decreased over time after 3–6 months: 0–3 months, 64% (101/158); >3–6 months, 63% (86/137); >6–9 months, 47% (54/114); >9–12 months, 52% (52/100), and seldom led to discontinuation of duvelisib (≤10%). Dose reductions can contribute to the effective management of TEAEs with duvelisib.

*Permanently reduced dose.

†Initiated treatment at doses <420 mg (47% 140 mg daily and 53% 280 mg daily).

‡Dose reduction in the first 8 weeks of initiating therapy.

§At least one dose reduction required.

This literature is derived from the publications which met selection criteria for discontinuation and interruption of treatment; however, dose reduction was not included as a search term, therefore there are likely to be more published articles that discuss the impact of dose reduction on survival.

AESI, adverse event of special interest; AF, atrial fibrillation; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; HR, hazard ratio; NHL, non-Hodgkin lymphoma; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients; TEAE, treatment emergent adverse event.

Table S6. Venetoclax dose reduction in the event of specific hematologic toxicity within the MURANO study (protocol guidelines).

Venetoclax current dose level	**Venetoclax dose reduction**
400 mg	200 mg
200 mg	100 mg
100 mg	Discontinue venetoclax and rituximab

Table S7. Baseline demographic predictors (logistic regression model) for incidence of neutropenia.

	Venetoclax related neutropenia		Venetoclax non-related neutropenia	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (≥65 *vs* <65 years)	0.5 (0.2–1.4)	0.1770	0.3 (0.1–1.9)	0.2054
Sex (female *vs* male)	2.8 (1.0–8.1)	0.0516	0.3 (0.0–3.3)	0.3218
Race (white *vs* non-white)	0.3 (0.0–3.6)	0.3208		
Chromosome 11q deletion (abnormal *vs* normal)	0.8 (0.3–2.2)	0.7227	0.5 (0.1–3.5)	0.4752
***TP53* mutation** (mutated *vs* unmutated)	1.9 (0.6–6.4)	0.2770	1.7 (0.2–13.3)	0.6086
IGVH (mutated *vs* unmutated)	5.2 (1.7–16.3)	0.0044	7.1 (1.0–52.2)	0.0543
Beta-2 microglobulin (>3.5 *vs* ≤3.5 mg/L)	2.2 (0.7–7.0)	0.1806	0.6 (0.1–4.2)	0.5717
Rai stage		0.2883		
Stage 1 *vs* 0	3.7 (1.0–13.7)			
Stage 2 *vs* 0	3.4 (0.9–13.6)			
Stage 3 *vs* 0	2.5 (0.5–14.1)			
Stage 4 *vs* 0	4.3 (0.8–23.7)			
Bulky disease (≥5 *vs* <5 cm)	2.7 (0.9–8.0)	0.0815	1.2 (0.2–9.5)	0.8438
Number of prior regimens (>1 *vs* 1)	2.8 (1.2–6.9)	0.0235	0.1 (0.0–1.3)	0.0764
Response duration to most recent prior therapy (≥12 *vs* <12 months)	1.2 (0.4–3.5)	0.6824	0.1 (0.0–1.0)	0.0537
Renal impairment status		0.4639		
Mild *vs* normal	0.6 (0.2–1.6)			
Moderate *vs* normal	0.9 (0.2–4.8)			
Hepatic impairment status		0.2568		
Mild *vs* normal	0.4 (0.1–1.3)			
Moderate/severe *vs* normal	1.5 (0.3–8.0)			

CI, confidence interval; IGVH, immunoglobulin heavy chain gene mutation.

Table S8. Baseline demographic predictors (logistic regression model) for GI toxicity.

	Venetoclax related GI toxicity		Venetoclax non-related GI toxicity	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (≥65 *vs* <65 years)	0.6 (0.2–1.6)	0.2711	3.8 (1.2–11.7)	0.0211
Sex (female *vs* male)	1.0 (0.4–2.7)	0.9841	0.5 (0.2–1.6)	0.2440
Race (white *vs* non-white)	1.2 (0.1–19.8)	0.8849	1.4 (0.1–25.1)	0.8099
Chromosome 11q deletion (abnormal *vs* normal)	0.7 (0.3–1.8)	0.4480	1.3 (0.5–3.5)	0.6263
***TP53* mutation** (mutated *vs* unmutated)	0.6 (0.2–1.9)	0.3813	0.9 (0.3–3.1)	0.8503
IGVH (mutated *vs* unmutated)	2.2 (0.7–6.3)	0.1583	1.9 (0.6–5.8)	0.2588
Beta-2 microglobulin (>3.5 *vs* ≤3.5 mg/L)	1.8 (0.6–5.5)	0.2778	0.5 (0.2–1.6)	0.2233
Rai stage		0.4137		0.9721
Stage 1 *vs* 0	1.2 (0.3–4.1)		0.9 (0.2–3.5)	
Stage 2 *vs* 0	0.5 (0.1–2.1)		1.0 (0.2–4.2)	
Stage 3 *vs* 0	2.4 (0.5–12.7)		0.6 (0.1–4.4)	
Stage 4 *vs* 0	0.7 (0.2–3.6)		0.7 (0.1–4.5)	
Bulky disease (≥5 *vs* <5 cm)	2.3 (0.8–6.4)	0.1314	1.5 (0.5–4.7)	0.4823
Number of prior regimens (>1 *vs* 1)	1.2 (0.5–2.9)	0.6527	0.7 (0.3–1.8)	0.4556
Response duration to most recent prior therapy (≥12 *vs* <12 months)	3.6 (1.3–10.2)	0.0160	0.6 (0.2–1.6)	0.2844
Renal impairment status		0.0493		0.2926
Mild *vs* normal	2.7 (1.0–7.4)		0.7 (0.2–2.1)	
Moderate *vs* normal	7.1 (1.4–36.7)		0.2 (0.0–1.6)	
Hepatic impairment status		0.1298		
Mild *vs* normal	0.6 (0.2–1.9)			
Moderate/severe *vs* normal	4.8 (0.8–29.0)			

CI, confidence interval; GI, gastrointestinal; IGVH, immunoglobulin heavy chain gene mutation.