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Safety of Extended Pirtobrutinib Exposure in Relapsed and/or Refractory B-Cell Malignancies.

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## Fixed-Duration Pirtobrutinib plus Venetoclax with or without Rituximab in Relapsed/Refractory CLL: Phase 1b BRUIN Trial

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### Abstract:

Pirtobrutinib is a highly selective, non-covalent (reversible) Bruton tyrosine kinase inhibitor (BTKi). Patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) were treated with fixed-duration pirtobrutinib plus venetoclax (PV) or pirtobrutinib plus venetoclax and rituximab (PVR) in this phase 1b trial (NCT03740529). Prior covalent BTKi therapy was allowed, but not prior venetoclax. Patients were assigned to receive PV (n=15) or PVR (n=10) for 25 cycles. Median age was 66 years (range, 39-78). Median prior lines of therapy was 2 (range, 1-4), and 17 (68%) patients had received prior covalent BTKi. At the data-cutoff date (May 5, 2023), median time on study was 27.0 months for PV and 23.3 months for PVR. Overall response rates were 93.3% (95% CI:68.1-99.8%) for PV and 100% (95% CI:69.2-100.0%) for PVR, with 10 complete responses (PV:7; PVR:3). After 12 cycles of treatment, 85.7% (95% CI:57.2-98.2%) of PV and 90.0% (95% CI:55.5-99.7%) of PVR patients achieved undetectable minimal residual disease assessed in peripheral blood by clonoSEQ® assay at a sensitivity of <math>1 \times 10^{-4}</math>. Progression-free survival at 18 months was 92.9% (95% CI: 59.1-99.0) for PV patients and 80.0% (95% CI: 40.9-94.6) for PVR patients. No DLTs were observed in either treatment combination during the 5-week assessment period. The most common grade {greater than or equal to}3 adverse events for all patients included neutropenia (52%) and anemia (16%). Adverse events led to dose reduction in 3 patients and discontinuation in 2. In conclusion, fixed-duration PV or PVR was well tolerated and had promising efficacy in patients with R/R CLL, including patients previously treated with a covalent BTKi.-

**Conflict of interest:** COI declared - see note

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**Agreement to Share Publication-Related Data and Data Sharing Statement:** Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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# Fixed-Duration Pirtobrutinib plus Venetoclax with or without Rituximab in Relapsed/Refractory CLL: Phase 1b BRUIN Trial

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## Data sharing

Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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## KEY POINTS

- Pirtobrutinib plus venetoclax ± rituximab was tested in relapsed/refractory CLL, including after progression on a covalent BTK inhibitor
- These fixed-duration treatments were safe and showed promising efficacy in both covalent BTK-naïve and BTK-exposed patients

## ABSTRACT

Pirtobrutinib is a highly selective, non-covalent (reversible) Bruton tyrosine kinase inhibitor (BTKi). Patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) were treated with fixed-duration pirtobrutinib plus venetoclax (PV) or pirtobrutinib plus venetoclax and rituximab (PVR) in this phase 1b trial (NCT03740529). Prior covalent BTKi therapy was allowed, but not prior venetoclax. Patients were assigned to receive PV (n=15) or PVR (n=10) for 25 cycles. Median age was 66 years (range, 39–78). Median prior lines of therapy was 2 (range, 1–4), and 17 (68%) patients had received prior covalent BTKi. At the data-cutoff date (May 5, 2023), median time on study was 27.0 months for PV and 23.3 months for PVR. Overall response rates were 93.3% (95% CI:68.1–99.8%) for PV and 100% (95% CI:69.2–100.0%) for PVR, with 10 complete responses (PV:7; PVR:3). After 12 cycles of treatment, 85.7% (95% CI:57.2–98.2%) of PV and 90.0% (95% CI:55.5–99.7%) of PVR patients achieved undetectable minimal residual disease assessed in peripheral blood by clonoSEQ® assay at a sensitivity of  $<1 \times 10^{-4}$ . Progression-free survival at 18 months was 92.9% (95% CI: 59.1-99.0) for PV patients and 80.0% (95% CI: 40.9-94.6) for PVR patients. No DLTs were observed in either treatment combination [during the 5-week assessment period](#). The most common grade ≥3 adverse events for all patients included neutropenia (52%) and anemia (16%). Adverse events led to dose reduction in 3 patients and discontinuation in 2. In conclusion, fixed-duration PV or PVR was well tolerated and had promising efficacy in patients with R/R CLL, including patients previously treated with a covalent BTKi.

## INTRODUCTION

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are chronic malignancies characterized by clonal proliferation of mature B cells. For many years, chemotherapy in combination with an anti-CD20 monoclonal antibody was the cornerstone of early treatment options for patients with CLL/SLL, but standard treatments now mainly consist of targeted therapies, including the covalent Bruton tyrosine kinase (BTK) inhibitors ibrutinib, acalabrutinib, and zanubrutinib<sup>1-3</sup> and the BCL-2 inhibitor venetoclax.<sup>4-6</sup> While monotherapies with targeted agents have improved the outcomes of patients with CLL/SLL, combination strategies have emerged to address some of the limitations of single-agent therapy.<sup>7</sup>

Covalent BTK inhibitors as single agents have been administered until toxicity or disease progression.<sup>8</sup> Despite improvements in survival, the covalent BTK inhibitors alone rarely achieve a complete response or undetectable minimal residual disease (uMRD), thus necessitating their continuous administration to maintain efficacy.<sup>9</sup> A major drawback of continuous dosing has been the potential for cumulative adverse events (AEs) that may negatively impact quality of life as well as the ability to adhere to treatment, and thereby may compromise the durability of disease control and outcomes for patients.<sup>10,11</sup> Up to 40% of patients discontinue ibrutinib, primarily because of drug-related toxicity.<sup>12</sup> Importantly, while both acalabrutinib and zanubrutinib have demonstrated lower incidences of grade 3 or higher AEs than ibrutinib (acalabrutinib: 68.8% vs 74.9%; zanubrutinib: 67.3% vs 70.4%, respectively), approximately 15% of patients still discontinued acalabrutinib or zanubrutinib due to drug-related AEs. These AEs occurred during a median treatment duration of approximately 38 months for acalabrutinib and 28 months for zanubrutinib.<sup>2,13</sup>

Another challenge associated with continuous treatment with a covalent BTK inhibitor remains acquired treatment resistance and consequent disease progression, <sup>14,15</sup> whereas

fixed-duration regimens may be less likely to generate such resistance mutations.<sup>16</sup> In addition, surveys of adults with CLL indicate that often patients prefer fixed-duration treatment regimens over continuous dosing.<sup>17-19</sup> Clinical trials of venetoclax combined with an anti-CD20 antibody demonstrated that a fixed-duration treatment strategy was a viable option.<sup>4,5</sup> Furthermore, venetoclax combined with covalent BTK inhibitors in doublet fixed-duration regimens also have shown promising efficacy in both phase 2 and 3 trials.<sup>20-24</sup> More recently, fixed-duration triplet regimens combining venetoclax, a covalent BTK inhibitor, and an anti-CD20 antibody have demonstrated promising outcomes; however, these triplet combinations have not been proven to be superior to doublet combinations.<sup>25-27</sup> Additionally, the adverse event profiles of these regimens are an important consideration that may limit their use. Cardiac events occurred more commonly among patients treated with the combination of venetoclax and ibrutinib, likely due to ibrutinib, than among patients treated with chemoimmunotherapy.<sup>21,23,28</sup> Cytopenias were less common with venetoclax and ibrutinib than chemoimmunotherapy, and infection rates varied across studies and were either comparable or slightly higher with venetoclax and ibrutinib than chemoimmunotherapy.<sup>21,29</sup> In contrast, infection rates were higher with ibrutinib, venetoclax, and obinutuzumab than venetoclax and an anti-CD20 antibody.<sup>27</sup> Single-arm studies of triplet combinations have demonstrated a risk of cytopenias, in addition to adverse events reported with monotherapy, such as headache, fatigue, bruising, nausea, diarrhea, infusion-related reactions, hypertension, arthralgias, and infection.<sup>30</sup>

Pirtobrutinib is a noncovalent (reversible) BTK inhibitor that demonstrates low-nanomolar potency against both wild-type and C481-mutant BTK, the most common mutation associated with resistance to covalent BTK inhibitors.<sup>31</sup> Pirtobrutinib monotherapy is administered continuously until toxicity or disease progression. In the BRUIN phase 1/2 clinical trial, 247 patients with CLL/SLL who had previously received a covalent BTK inhibitor were treated with continuous pirtobrutinib monotherapy and had an overall response rate of 82.2%.<sup>32</sup> Treatment



with pirtobrutinib monotherapy was associated with mainly low-grade AEs. The most common grade 3 or higher AEs were infections (28.1%) and neutropenia (26.8%). The incidences of grade 3 or higher atrial fibrillation (1.3%), major hemorrhage (2.2%), and hypertension (3.5%) were low. AEs were manageable leading to low dose reduction and treatment discontinuation rates (4.7% and 2.8%, respectively). This favorable safety profile is consistent with pirtobrutinib's high degree of BTK selectivity and minimal off-target inhibition.<sup>33</sup> On the basis of these findings, pirtobrutinib monotherapy was approved in 2023 by the US Food and Drug Administration for the treatment of adults with CLL/SLL who have received at least two prior lines of systemic therapy, including a BTK inhibitor and a BCL-2 inhibitor.<sup>34,35</sup>

The observed safety profile and clinical activity of pirtobrutinib monotherapy makes pirtobrutinib an attractive candidate to combine with venetoclax and anti-CD20 antibodies. In this phase 1b clinical trial, we evaluated the safety and efficacy of fixed-duration pirtobrutinib in combination with either venetoclax (PV) or venetoclax and rituximab (PVR) in patients with previously treated CLL/SLL, including those who had received a covalent BTK inhibitor.

## **METHODS**

### **Study design and treatment**

The primary objective of the phase 1b portion of the BRUIN trial was to evaluate the safety of fixed-duration pirtobrutinib plus venetoclax, with or without rituximab, in adults with relapsed or refractory CLL/SLL. The first 6 patients were enrolled in each cohort according to a 3 + 3 design to determine the safety of combination treatments. Patients received treatment for 25 cycles or until disease progression, unacceptable toxicity, or withdrawal. Each treatment cycle was 28 days. Briefly, starting in cycle 1, oral pirtobrutinib was given daily at the approved dose of 200 mg.<sup>36</sup> Venetoclax and rituximab delivery were each based on the labelled CLL dose.<sup>37,38</sup> To minimize the risk of tumor lysis syndrome (TLS), the first treatment cycle consisted

of pirtobrutinib (with or without rituximab) to debulk the tumor before initiation of venetoclax. Venetoclax started in cycle 2 at 20 mg/day and escalated weekly over 5 weeks to the target dose of 400 mg/day, as per the standard ramp-up schedule. Rituximab was administered intravenously at 375 mg/m<sup>2</sup> for cycle 1 and then at 500 mg/m<sup>2</sup> for cycles 2-6. Both pirtobrutinib and venetoclax were given in combination through cycle 25, for a total of 24 cycles. After treatment discontinuation, patients were followed approximately every 3 months for up to 2 years.

The study was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. The protocol was approved by institutional review boards or independent ethics committees of all participating institutions. All patients provided written informed consent. This study was registered with ClinicalTrials.gov (NCT03740529).

### **Patient eligibility**

Adults (≥18 years) were eligible for this study if they had relapsed or refractory CLL/SLL and if venetoclax or venetoclax plus rituximab would be an appropriate treatment. Prior anti-CD20 antibody and/or covalent BTK inhibitor therapy was allowed; however, prior BCL-2 inhibitor use was not permitted. Other eligibility criteria included adequate hematologic status within 7 days of starting study treatment; Eastern Cooperative Oncology Group (ECOG) status of 0–2; and adequate hepatic and renal function. Patients were excluded if they had received a hematopoietic stem cell transplant or chimeric antigen receptor T cell therapy within 60 days prior to starting study treatment. Patients were also excluded if they had known central nervous system involvement, significant cardiovascular disease, history of a major bleeding event with a prior BTK inhibitor, or current prescription for warfarin. Patients currently receiving anticoagulation therapy with warfarin were excluded, but other anticoagulants or antiplatelets

were allowed. Baseline mutations in *TP53*, *BTK*, and *PLCG2* were assessed using targeted next-generation sequencing panels (NeoGenomics Laboratories, Inc., Fort Myers, FL). The presence of *TP53* mutation had a limit of detection of 5% variant allele frequency.

### **Safety assessment**

The primary endpoint was safety as assessed by the frequency and severity of adverse events (AEs). AEs were graded according to the Common Terminology Criteria for Adverse Events, version 5.0. AEs were coded using the Medical Dictionary for Regulatory Activities, version 24.0. The dose-limiting toxicity (DLT) assessment period occurred from the first administration of all agents in the combination regimen through the first 5 weeks of treatment (i.e., cycle 2 day 1 to cycle 3 day 8). DLT was defined as any grade  $\geq 3$  non-hematologic or hematologic toxicity (with exceptions as defined in the Supplemental Methods) or any grade toxicity resulting in discontinuation, dose reduction, with less than 75% of planned doses. For a combination to be considered safe for further study, a DLT rate  $< 33\%$  was required (i.e., 0 of 3 or 1 of 6 patients). A Safety Review Committee determined whether additional patients or doses should be evaluated based on the DLT rate in the first 6 enrolled patients receiving combination treatment. If the Safety Review Committee deemed the initial dose safe for the first 6 enrolled patients, additional patients could be enrolled to each dosing combination at this dose to further investigate tolerability, efficacy, and pharmacokinetics (PK). Patients were first enrolled to receive PV to assess the safety of dual combination treatment. After PV was deemed safe in the first 3 patients who completed the DLT assessment period, patients were then enrolled to receive PVR. The final enrolled number of patients who received PV (n=15) or PVR (n=10) was considered reasonable to gain preliminary assessment of the primary endpoint of safety.

Tolerability of pirtobrutinib was assessed by relative dose intensity and calculated by dividing the actual dose intensity (mg/day) by the planned dose intensity (mg/day) until treatment discontinuation.

## **Efficacy assessment**

Secondary efficacy endpoints included overall response rate (ORR), best overall response (BOR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and uMRD rate. All response endpoints were assessed by investigators according to criteria from the 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL).<sup>39</sup> ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR). Response assessments were performed by computed tomography every 2 cycles for the first year, every 3 cycles for the second year, and every 6 months thereafter. Hematologic or radiologic CRs were confirmed by bone marrow biopsy. Baseline molecular characteristics were assessed centrally. Blood was collected to assess MRD at screening, every 2 cycles from cycle 3 to cycle 12, and then every 3 cycles from cycle 13 to cycle 25. uMRD in peripheral blood was defined as <1 CLL cell per 10000 nucleated cells ( $10^{-4}$  sensitivity) via clonoSEQ assay (Adaptive Biotechnologies, Seattle WA).<sup>40</sup> The PK of pirtobrutinib and venetoclax were evaluated for the two combination treatments. Blood samples were collected serially for PK analyses on cycle 1 day 8, cycle 2 day 8, cycle 3 day 8, and cycle 4 day 1.

## **Statistical analysis**

The data-cutoff date for safety and efficacy analyses was May 5, 2023. Safety and efficacy were assessed in all patients who received at least 1 dose of study drug. Descriptive statistics were used to summarize the findings. ORR was calculated with a two-sided 95% confidence interval (CI) based on the exact binomial distribution. Distributions of time-to-event endpoints were estimated using the Kaplan-Meier method. SAS (version 9.4) was used for statistical analyses.

The data-cutoff date for PK analyses was February 5, 2023. PK analysis of pirtobrutinib and venetoclax was performed using non-compartmental methods in Phoenix version 8.3.5 (Certara, Princeton, NJ). Using Phoenix, the following PK parameters were calculated from

plasma concentrations if appropriate: maximum drug concentration ( $C_{max}$ ), time to maximum plasma concentration ( $T_{max}$ ), area under the concentration versus time curve from time 0 to  $t$  ( $AUC_{0-t}$ ), AUC from time 0 extrapolated to infinity ( $AUC_{0-\infty}$ ), clearance or apparent oral clearance, volume of distribution or apparent volume of distribution, and terminal elimination half-life. Descriptive statistics were used to summarize PK data.

## RESULTS

### Study population and disposition

Between August 2020 and July 2021, 25 patients with CLL in the United States and Australia were enrolled to receive treatment with PV ( $n=15$ ) or PVR ( $n=10$ ) (**Table 1**). No patients with SLL were enrolled. The median age for all patients was 66 years (range, 39–78). Most patients were male (PV: 87%; PVR: 70%). The median prior lines of therapy for all patients was 2 (range, 1–4). All patients had an ECOG functional performance status of either 0 (56%) or 1 (44%). The majority of patients had received previous treatment with an anti-CD20 antibody therapy (72%), covalent BTK inhibitor therapy (68%), and chemotherapy (56%). Among the 17 patients who received a previous covalent BTK inhibitor, 12 (71%) had discontinued treatment of the prior BTK inhibitor because of progressive disease and the other 5 (29%) because of toxicity. At baseline, high-risk cytogenetic and molecular features among patients with available pretreatment peripheral blood samples for central assessment identified *BTK* C481 mutation in 9/23 (39%), *PLCG2* mutation in 1/23 (4.3%), 17p deletion in 4/20 (20%), *TP53* mutation in 6/23 (26%), both 17p deletion and/or *TP53* mutation in 7/19 (36.8%), 11q deletion in 8/20 (40%), and unmutated *IGHV* in 16/20 (80%) patients (**Table 1**).

At the time of the data cutoff, median time on treatment was 23.0 months (interquartile range [IQR], 22.0–23.3) for all patients, 22.8 (IQR, 20.5–23.1) months for PV, and 23.0 (IQR, 21.9–23.3) months for PVR. Median time on study was 25.2 months (IQR, 23.3–28.3) for all

patients, 27.0 (IQR, 24.7–32.1) months for PV, and 23.3 (IQR, 21.9–24.2) months for PVR. As of the data cutoff, treatment was ongoing (>21 months) in 3 patients (PV: 1; PVR: 2) and had been discontinued in 22 patients (PV: 14; PVR: 8). Of these 22 patients, 14 (PV: 9, PVR: 5) completed all 24 cycles of combination therapy. Treatment was discontinued early in 8 patients (PV: 5; PVR: 3) due to progressive disease (PV: 2), AEs (PVR: 2), death due to AE that was considered unrelated to treatment by the investigator (PVR: 1), or other reasons (PV: 3) (**Supplemental Table 1**). Three additional deaths occurred, one after discontinuing treatment for PD, one after discontinuing treatment for AE, and one after the completion of the planned 25 cycles of therapy

## Safety

No DLTs were observed in either treatment combination during the per protocol 5-week observation period for DLTs. The incidence of DLTs during 8 weeks of combination treatment was also reviewed in the first 6 patients treated with PV or PVR, and no DLTs were observed. Two cases of grade  $\geq 3$  neutrophil count decrease (PV: 1; PVR: 1) were observed during this 8-week period, which did not meet the DLT criteria. All TEAEs within 12 months after initial dose of venetoclax were retrospectively analyzed for the first 6 patients in each cohort for further safety validation. Seven AEs that would have been classified as DLTs were observed among 3 patients. One patient experienced grade 5 COVID-19 pneumonia; one patient experienced grade 3 cerebral hemorrhage, diabetic ketoacidosis, and grade 5 cardiac failure; and one patient experienced grade 3 back pain, bone pain, and non-cardiac chest pain. All patients were receiving PVR, and only the grade 3 cerebral hemorrhage was deemed related to treatment. The median relative dose intensity for all patients was 98.4% for pirtobrutinib, 98.4% for venetoclax, and 100% for rituximab. The most common AEs and AEs of special interest (i.e., those previously associated with BTK inhibitors) are shown in **Tables 2 and 3**, respectively. The most common all-cause AEs were nausea (60%), fatigue (53%), neutropenia (47%), and

diarrhea (47%) for patients receiving PV and neutropenia (70%), diarrhea (60%), fatigue (50%), and nausea (40%) for patients receiving PVR. Neutropenia was the most common all-cause grade  $\geq 3$  AE (PV: 47%; PVR: 60%). All-cause grade  $\geq 3$  AEs of special interest included hypertension (PV: 7%; PVR: 10%), bleeding (PV: 0%; PVR: 10%), and serious infections (PV: 27%; PVR: 40%). No atrial arrhythmias were observed. With the exception of neutropenia, treatment-related grade  $\geq 3$  AEs were uncommon. One PV patient developed grade 4 TLS during dose escalation to venetoclax 400 mg (**Supplemental Results**). Symptoms resolved after intravenous fluids and temporary dialysis for refractory hyperkalemia, and the patient achieved the planned venetoclax target dose of 400 mg daily by cycle 3 day 1 and completed all 24 cycles of combination therapy at this dose.

Treatment-related dose reductions occurred in 3 patients (PV:1; PVR: 2). The dose of pirtobrutinib for the patient in the PV group was reduced because of diarrhea and platelet count decreased. Doses of both pirtobrutinib and venetoclax were reduced in 2 patients in the PVR group because of platelet count decreased in one case and neutropenia in the other. Neutropenia also led to dose interruptions in 7 patients (PV: 5; PVR: 2) and was treated with growth-factor support in 10 patients (PV: 4; PVR: 6). Treatment was discontinued early in 2 patients because of treatment-related neutropenia or urinary tract infection (PV: 0; PVR: 2) (**Supplemental Table 1**). No treatment-related discontinuations or deaths were observed among patients receiving PV.

## **Efficacy**

All 25 patients were evaluable for efficacy, and the ORR was 96.0% (95%CI: 79.6–99.9), with 10 CRs and 14 PRs (**Table 4**). ORR was 93.3% (95% CI, 68.1–99.8) for the 15 patients receiving PV, and 100% (95% CI, 69.2–100.0) for the 10 patients receiving PVR. CR rates were 46.7% (95% CI: 21.3–73.4%) for patients receiving PV and 30.0% (95% CI: 6.7–61.3%) for patients receiving PVR. Overall, 17 patients had previously been treated with a covalent BTK

inhibitor, and 8 were naïve to BTK inhibitor therapy. Among the patients with prior exposure to a BTK inhibitor, 8 achieved CR and 9 PR, and among those who were BTK inhibitor naïve, 2 achieved CR, 5 PR, and 1 SD. Nine patients had a BTK C481s mutation, with 4 achieving CR and 5 PR. The one patient with a PLCG2 mutation achieved CR. Overall median time to best response was 2.4 months (IQR, 1.9–14.3), corresponding to the time of the first disease assessment. Tumor size of target lesions decreased by at least 50% from baseline for 96% of patients and by at least 75% from baseline for 84% of patients (**Figure 1**). The decrease in tumor size by at least 75% was similar among the 17 patients previously treated with a BTK inhibitor (88%) and the 8 patients who were BTK inhibitor naïve (75%) (**Figure 1**). Median duration of follow-up for response was 20.3 (IQR: 18.4–21.2) months for all patients, 20.3 (IQR: 18.4–23.9) months for PV patients, and 20.3 (IQR: 18.9–20.3) months for PVR patients. Duration of response estimates at 18 months were 87.5% (95% CI: 66.1–95.8%) for all patients, 92.9% (95% CI: 59.1–99.0%) for PV patients, and 80.0% (95% CI: 40.9–94.6%) for PVR patients.

Median duration of follow-up for PFS was 22.1 (IQR: 20.1–23.0) months for all patients, 22.1 (IQR: 20.1–25.7) for PV, and 22.1 (IQR: 20.7–22.1) for PVR. Median PFS and OS was not reached for either the doublet or triplet combination. PFS and OS estimates at 24 months for all 25 patients were 79.5% (95% CI: 52.0–92.3) and 87.5% (95% CI: 66.1–95.8), respectively. PFS and OS estimates at 24 months for PV were 79.6% (95% CI: 37.1–94.9) and 92.9% (95% CI: 59.1–99.0), respectively (**Figure 2A and 2C**). The PFS estimate at 24 months for PVR patients was not evaluable, while the PFS estimate at 18 months was 80.0% (95% CI 40.9–94.6%), and the OS estimate at 24 months was 80.0% (95%CI: 40.9–94.6) (**Figure 2B and 2D**).

## MRD

Twenty-four patients were evaluable for MRD assessment in peripheral blood (PV: 14; PVR: 10). Median time-to-first uMRD, assessed at a sensitivity threshold of  $10^{-4}$ , was 4.3



months for patients receiving PV (n=14) and 3.7 months for patients receiving PVR (n=10). The uMRD rate after completion of cycle 12 was 70.8% for 24 evaluable patients, including 67% of patients receiving PV and 70% of patients receiving PVR (**Figure 3**). During treatment, uMRD was achieved by 85.7% (95% CI: 57.2–98.2) of patients receiving PV and 90.0% (95% CI: 55.5–99.7) of patients receiving PVR (**Figure 3**). Among patients who achieved uMRD, all except one sustained their uMRD status during subsequent MRD assessments (**Figure 3**). To evaluate the depth of MRD response, the uMRD rate was also assessed at sensitivity thresholds of  $10^{-5}$  and  $10^{-6}$ . At the  $10^{-5}$  threshold, uMRD was achieved by 79.2% (95%CI: 57.8–92.9) of all patients, 78.6% (95% CI: 49.2–95.3) of PV patients, and 80.0% (95% CI: 44.4–97.5) of PVR patients (**Figure 3**). At the  $10^{-6}$  threshold, uMRD was achieved by 62.5% (95% CI: 40.6–81.2) of all patients, 57.1% (95% CI: 28.9–82.3) of PV patients, and 70.0% (95% CI: 34.8–93.3) of PVR patients (**Figure 3**).

Twelve patients (PV: 6; PVR: 6) who achieved uMRD ( $10^{-4}$ ) were classified as partial responders, either due solely to residual lymphadenopathy (n=8) or pending bone marrow biopsy for CR confirmation (n=4). Of these 12 patients, 7 achieved deep levels of uMRD ( $10^{-6}$ ), including 3 with residual lymphadenopathy and 4 patients who met the iwCLL criteria for CR but were pending confirmation of normal bone marrow. With the limited number of patients, there was no clear association between uMRD and timing or depth of response.

### Pharmacokinetics

For those receiving PV, 260 pirtobrutinib samples and 120 venetoclax samples from 14 patients were included in the PK analysis. For those receiving PVR, 198 pirtobrutinib samples and 98 venetoclax samples from 10 patients were included in the PK analysis. Pirtobrutinib and venetoclax pharmacokinetics were similar in both combination regimens, suggesting that addition of rituximab did not affect the PK of either pirtobrutinib or venetoclax (**Figure 4**;

**Supplemental Tables 2 and 3).** There was no apparent drug-drug interaction between pirtobrutinib and venetoclax.

## DISCUSSION

Fixed-duration combination treatments with covalent BTK inhibitors and venetoclax have achieved deep remissions and long-term disease control in patients with CLL/SLL; however, the real-world utility of these regimens has been limited. Moreover, in the modern era, many patients receive covalent BTK inhibitors as frontline continuous therapy, making their use in combination regimens significantly less relevant in the relapsed setting. In this phase 1b trial, the non-covalent (reversible) BTK inhibitor pirtobrutinib demonstrated promising activity when combined with venetoclax, with or without rituximab, in patients with relapsed/refractory CLL. Among all patients treated with PV or PVR, the ORR was 96.0%, including 40% of patients who achieved a CR, and the PFS at 24 months was 79.5%. Notably, these clinical responses were seen in patients who were previously treated with covalent BTK inhibitors (68%), most of whom had developed covalent BTKi resistance (71%). In addition, the uMRD ( $<10^{-4}$ ) rate in peripheral blood after 12 cycles as measured by next-generation sequencing was 70.8% for patients receiving PV or PVR. Moreover, uMRD ( $<10^{-4}$ ) was achieved in 87.5% of patients at some time during the trial. Early treatment discontinuation due to disease progression was rare, occurring in 2 patients receiving PV. In addition, PK analyses indicated that there were no apparent drug-drug interactions between pirtobrutinib and venetoclax. Both combination therapies had PK exposures comparable to pirtobrutinib and venetoclax monotherapies.<sup>34,37</sup> Taken together, these findings demonstrate that pirtobrutinib combined with venetoclax, with or without rituximab, has promising efficacy in patients with R/R CLL, including those who were previously treated with a covalent BTK inhibitor.

Fixed-duration pirtobrutinib-based combination therapies were also well tolerated. Observed AEs were consistent with those seen with pirtobrutinib, venetoclax, and rituximab monotherapy. Among the 22 patients who had discontinued study treatment at the time of data cutoff, early treatment discontinuation due to AEs was relatively uncommon (9%). Moreover, the

tolerability of pirtobrutinib-based combination treatments led to high rates of patient adherence to treatment as evidenced by relative dose intensities for all study drugs of 98% or higher. Collectively, these data suggest that pirtobrutinib combined with venetoclax with or without rituximab was well tolerated in patients with R/R CLL.

Achieving uMRD, defined as <1 CLL cell per 10,000 leukocytes, during or after fixed-duration treatment has been shown to predict more favorable PFS and OS.<sup>39,41</sup> Comparing uMRD results of clinical trials of different fixed-duration combination treatments can be challenging, however. Sample source (peripheral blood or bone marrow), time of assessment, depth of assessment, and assay technique can influence the estimated rate of MRD. In this phase 1b trial, MRD was assessed using next-generation sequencing (clonoSEQ assay) at three thresholds ( $10^{-4}$ ,  $10^{-5}$ , and  $10^{-6}$ ) in peripheral blood at various times during treatment. During treatment, uMRD ( $10^{-4}$ ) was achieved by 85.7% of patients receiving PV and 90.0% of patients receiving PVR. Many clinical trials have shown that venetoclax combined with a covalent BTK inhibitor can achieve high rates of uMRD and induce deep remissions that are maintained after stopping treatment.<sup>20,22-24,29,42,43</sup> Unlike patients in these trials, however, the majority of patients in this phase 1b trial had been previously treated with a covalent BTK inhibitor, suggesting that pirtobrutinib-based combination treatments can achieve deep remissions in relapsed CLL patients even after treatment failure on a covalent BTK inhibitor. Whether MRD can be utilized to select patients who would benefit from shorter or longer durations of fixed therapy remains an ongoing research question.

These results may compare relatively favorably to results from the phase 3 MURANO trial.<sup>5</sup> In MURANO, fixed-duration venetoclax and rituximab were given to previously treated patients with relapsed or refractory CLL. After patients had completed 12 cycles of treatment, uMRD ( $<10^{-4}$ ) was 60% in peripheral blood. For PV or PVR, the peripheral blood uMRD ( $<10^{-4}$ ) rate was 70.8% after 12 cycles of treatment. A notable distinction between the MURANO study

and this trial lies in the patient population. In MURANO, very few patients had prior exposure to a covalent BTK inhibitor. In contrast, the majority of patients in this phase 1b trial (68%; 17/25) had previous exposure to a covalent BTK inhibitor.

The CR rate (40%) observed in this phase 1b study was not concordant with the uMRD rate (87.5%). Four patients who achieved uMRD ( $10^{-4}$ ) were classified as partial responders pending bone marrow confirmation of CR. These patients met all other iwCLL criteria for CR. Moreover, all 4 patients achieved deep uMRD at the  $10^{-6}$  threshold. However, if morphologically normal bone marrow has not been confirmed, the best available response per the iwCLL criteria is PR. It is therefore possible that the absence of bone marrow assessment in these 4 patients may have led to an underestimation of the CR rate in this phase 1b study. In addition, 8 patients were classified as partial responders due solely to residual lymphadenopathy, and it is typical of most recent studies in CLL that the CR rate is lower than the rate of uMRD, usually because of small residual lymphadenopathy.

This study has important limitations. Our sample size was too small to meaningfully compare the relative tolerability and efficacy of PV and PVR regimens with each other or other treatments. Important differences between these combination regimens may include the mode of administration (e.g., intravenous for PVR vs oral for PV) and safety profile (e.g., infusion related reactions with PVR or possibly more TLS with PV due to less debulking). These treatment attributes may be important when selecting an optimal treatment for a patient. Several differences in baseline characteristics between treatment groups, including functional status, molecular features, and prior lines of therapy, may have influenced apparent differences in safety profiles and outcomes. Longer follow-up and large sample size are needed to establish the safety of fixed-duration treatment and better estimate the durability of responses. Additionally, the 5-week observation period for DLTs only included one week of full-dose venetoclax. Additional retrospective analysis of 28 days of combination therapy including full-

dose venetoclax and analysis of 12 months at the full dose of venetoclax further supports the safety of the current dose based on the 3+3 decision rule.

In summary, both fixed-duration PV and PVR were well tolerated and demonstrated sufficiently promising efficacy to warrant further investigation in patients with relapsed or refractory CLL. The BRUIN CLL-322 phase 3 trial comparing fixed-duration PVR to venetoclax and rituximab (VR) in previously treated CLL is ongoing (NCT04965493). In addition, other pirtobrutinib-based combinations are being explored in patients with previously untreated CLL (NCT05536349, NCT05677919). Plans are also underway to launch the phase 3 CLL18 trial, which will evaluate fixed-duration venetoclax plus obinutuzumab for 12 months, fixed-duration venetoclax plus pirtobrutinib for 15 months, and MRD-guided venetoclax plus pirtobrutinib for 15 to 36 months in patients with treatment-naïve CLL.

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## **Authorship contributions**

All authors critically revised the manuscript and approved the final version. DET conceptualized and designed the study. DET, BN, CW, XZ, SC, DL, DR, NM, and SM verified and interpreted acquired study data and did the analysis. CW and XZ conducted statistical analyses. LER, JAW, CYC, CCC, NNS, WGW, MRP, NL, and JRB acquired and interpreted the study data. All authors had access to and verified the data. All authors vouch for the completeness and accuracy of the data and adherence to the protocol. All authors agreed to the content of the manuscript and submission, and all authors had access to primary clinical trial data.

## **Disclosure of conflicts of interest**

LER has served as a consultant for AbbVie, Ascentage, AstraZeneca, Beigene, Janssen, Loxo Oncology, Pharmacyclics, Pfizer, TG Therapeutics, served as a CME speaker for DAVA, Curio, Medscape, and PeerView, holds minority ownership interest in Abbott Laboratories, received travel support from LOXO oncology, and has received research funding (paid to the institution)

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## TABLES

**Table 1: Patient characteristics at baseline**

	<b>PV (n=15)</b>	<b>PVR (n=10)</b>	<b>Total (N=25)</b>
Age in years, median (range)	66 (49-77)	69 (39-78)	66 (39-78)
Sex, n (%)			
Female	2 (13)	3 (30)	5 (20)
Male	13 (87)	7 (70)	20 (80)
ECOG PS			
0	7 (47)	7 (70)	14 (56)
1	8 (53)	3 (30)	11 (44)
Mutation status, n (%) <sup>a</sup>			
<i>BTK</i> C481 mutant	6 (40)	3 (38)	9 (39)
<i>BTK</i> C481 wildtype	9 (60)	5 (63)	14 (61)
<i>PLCG2</i> mutation status, n (%) <sup>b</sup>			
Yes	1 (6.7)	0 (0.0)	1 (4.3)
No	14 (93.3)	8 (100.0)	22 (95.7)
del(17p) by FISH, n (%) <sup>c</sup>			
Yes	1 (9)	3 (33)	4 (20)
No	10 (91)	6 (67)	16 (80)
<i>TP53</i> mutation status, n (%) <sup>d</sup>			
Mutated	3 (20)	3 (38)	6 (26)
Unmutated	12 (80)	5 (63)	17 (74)
del(17p) and/or <i>TP53</i> mutation status, n (%) <sup>e</sup>			
Yes	3 (27.3)	4 (50.0)	7 (36.8)
No	8 (72.7)	4 (50.0)	12 (63.2)
del(11q) by FISH, n (%) <sup>f</sup>			
Yes	4 (36)	4 (44)	8 (40)
No	7 (63)	5 (56)	12 (60)
<i>IGHV</i> mutation status, n (%) <sup>g</sup>			
Mutated	3 (27)	1 (11)	4 (20)
Unmutated	8 (73)	8 (89)	16 (80)
Prior lines of systemic therapy, median (range)			
All therapies	1 (1-2)	2 (1-4)	2 (1-4)
BTKi therapies	1 (0-1)	1 (0-2)	1 (0-2)
Prior Therapies, n (%)			
Anti-CD20 antibody <sup>h</sup>	11 (73)	7 (70)	18 (72)
BTKi	11 (73)	6 (60)	17 (68)
Chemotherapy	8 (53)	6 (60)	14 (56)
PI3K agent	1 (7)	2 (20)	3 (12)
Reasons for BTKi discontinuation, n (%) <sup>i</sup>			
Progressive disease	8 (73)	4 (67)	12 (71)
Toxicity	3 (27)	2 (33)	5 (29)

Total percentage might be different than the sum of the individual components due to rounding. Molecular features were analyzed by a central research laboratory. Percentages were calculated for patients with available data.

<sup>a</sup>2 patients had missing data (PV: 0; PVR: 2). <sup>b</sup>2 patients had missing data (PV: 0; PVR: 2). <sup>c</sup>5 patients had missing data (PV: 4; PVR: 1). <sup>d</sup>2 patients had missing data (PV: 0; PVR: 2). <sup>e</sup>6 patients had missing data (PV: 4; PVR: 2). <sup>f</sup>5

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patients had missing data (PV: 4; PVR: 1).<sup>9</sup>5 patients had missing data (PV: 4; PVR: 1).<sup>h</sup>Includes both patients who had anti-CD20 as monotherapy and as combination therapy. <sup>i</sup>Calculated as percent of patients who received prior BTK inhibitor. If more than one reason was noted for discontinuation, disease progression took priority.

Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy variable; PI3K, phosphatidylinositol 3-kinase; PV, pirtobrutinib plus venetoclax; PVR, pirtobrutinib, venetoclax, plus rituximab

**Table 2: Adverse events in 15 patients treated with PV**

AE	All-cause AEs ( $\geq 25\%$ ), %		Treatment-related AEs, %	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
Neutropenia <sup>a</sup>	7 (46.7)	7 (46.7)	7 (46.7)	7 (46.7)
Nausea	9 (60.0)	0 (0.0)	7 (46.7)	0 (0.0)
Fatigue	8 (53.3)	0 (0.0)	5 (33.3)	0 (0.0)
Diarrhea	7 (46.7)	2 (13.3)	4 (26.7)	2 (13.3)
Hypophosphatemia	5 (33.3)	0 (0.0)	2 (13.3)	0 (0.0)
Constipation	4 (26.7)	0 (0.0)	3 (20.0)	0 (0.0)
Cough	4 (26.7)	0 (0.0)	1 (6.7)	0 (0.0)
Platelet Count Decreased	4 (26.7)	1 (6.7)	4 (26.7)	1 (6.7)
Vomiting	4 (26.7)	0 (0.0)	2 (13.3)	0 (0.0)
<b>AEs of Interest<sup>b</sup></b>	<b>Any Grade</b>	<b>Grade <math>\geq 3</math></b>	<b>Any Grade</b>	<b>Grade <math>\geq 3</math></b>
Infections <sup>c</sup>	12 (80.0)	4 (26.7)	7 (46.7)	3 (20.0)
Arthralgia	4 (26.7)	0 (0.0)	2 (13.3)	0 (0.0)
Bruising <sup>d</sup>	3 (20.0)	0 (0.0)	3 (20.0)	0 (0.0)
Hypertension	3 (20.0)	1 (6.7)	2 (13.3)	0 (0.0)
Rash <sup>e</sup>	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Hemorrhage <sup>f</sup>	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Atrial Fibrillation/Flutter <sup>g</sup>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

<sup>a</sup>Aggregate of neutropenia and neutrophil count decreased. <sup>b</sup>AEs of interest are those that were previously associated with covalent BTK inhibitors regardless of occurrence rate. <sup>c</sup>Aggregate of all preferred terms indicating infection and including COVID-19. Infection-related grade 3-4 (no grade 5) AEs included COVID-19 pneumonia, pneumonia, oral candidiasis, sepsis, soft tissue infection, and abscess. <sup>d</sup>Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. <sup>e</sup>Aggregate of all preferred terms including rash. <sup>f</sup>Aggregate of all preferred terms including hemorrhage or hematoma. <sup>g</sup>Aggregate of atrial fibrillation and atrial flutter.

Abbreviations: AE, adverse events; BTKi, Bruton tyrosine kinase inhibitor; PV, pirtobrutinib plus venetoclax

**Table 3: Adverse events in 10 patients treated with PVR**

AE	All-cause AEs (≥25%), %		Treatment-related AEs, %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia <sup>a</sup>	7 (70.0)	6 (60.0)	7 (70.0)	6 (60.0)
Diarrhea	6 (60.0)	0 (0.0)	6 (60.0)	0 (0.0)
Fatigue	5 (50.0)	1 (10.0)	2 (20.0)	0 (0.0)
Nausea	4 (40.0)	0 (0.0)	4 (40.0)	0 (0.0)
Constipation	4 (40.0)	0 (0.0)	1 (10.0)	0 (0.0)
Infusion Related Reaction	4 (40.0)	2 (20.0)	4 (40.0)	2 (20.0)
Anemia	3 (30.0)	1 (10.0)	2 (20.0)	1 (10.0)
Back Pain	3 (30.0)	1 (10.0)	1 (10.0)	0 (0.0)
Chills	3 (30.0)	0 (0.0)	3 (30.0)	0 (0.0)
Dyspnoea	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry Mouth	3 (30.0)	0 (0.0)	1 (10.0)	0 (0.0)
<b>AEs of Interest<sup>b</sup></b>	<b>Any Grade</b>	<b>Grade ≥3</b>	<b>Any Grade</b>	<b>Grade ≥3</b>
Infections <sup>c</sup>	9 (90.0)	4 (40.0)	2 (20.0)	1 (10.0)
Bruising <sup>d</sup>	2 (20.0)	0 (0.0)	2 (20.0)	0 (0.0)
Rash <sup>e</sup>	3 (30.0)	0 (0.0)	1 (10.0)	0 (0.0)
Arthralgia	4 (40.0)	0 (0.0)	1 (10.0)	0 (0.0)
Hemorrhage <sup>f</sup>	2 (20.0)	1 (10.0)	1 (10.0)	1 (10.0)
Hypertension	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)
Atrial Fibrillation/Flutter <sup>g</sup>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

<sup>a</sup>Aggregate of neutropenia and neutrophil count decreased. <sup>b</sup>AEs of interest are those that were previously associated with covalent BTK inhibitors regardless of occurrence rate. <sup>c</sup>Aggregate of all preferred terms indicating infection and including COVID-19. Infection-related grade 3-4 (no grade 5) AEs included COVID-19, COVID-19 pneumonia, urinary tract infection, cellulitis, and cystitis. <sup>d</sup>Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. <sup>e</sup>Aggregate of all preferred terms including rash. <sup>f</sup>Aggregate of all preferred terms including hemorrhage or hematoma. <sup>g</sup>Aggregate of atrial fibrillation and atrial flutter.

Abbreviations: AE, adverse events; BTKi, Bruton tyrosine kinase inhibitor; PVR, pirtobrutinib, venetoclax, plus rituximab

**Table 4: Best overall response of pirtobrutinib-based combination treatments**

	PV (n=15)	PVR (n=10)	Total (N=25)
	15	10	25
<b>Overall response rate</b>			
% (95% CI)	93.3 (68.1-99.8)	100 (69.2-100)	96.0 (79.6-99.9)
<b>Best response, n (%)<sup>a</sup></b>			
CR	7 (46.7)	3 (30.0)	10 (40.0)
PR	7 (46.7)	7 (70.0)	14 (56.0)
SD	1 (6.7)	0	1 (4.0)
PD	0	0	0
<b>Time to best response</b>			
Median, months (IQR)	3.9 (1.9, 14.7)	1.9 (1.8, 10.7)	2.4 (1.9, 14.3)

Data-cutoff date of 05 MAY 2023.

<sup>a</sup>ORR is the number of patients with a best response of CR or PR divided by the total number of patients. Response status per iwCLL 2018 as assessed by the investigator.

Abbreviations: CI, confidence interval; CR, complete response; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; IQR, interquartile range; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PV, pirtobrutinib plus venetoclax; PVR, pirtobrutinib plus venetoclax plus rituximab; SD, stable disease



## FIGURES AND LEGENDS

### Figure 1: Change in tumor size from baseline to time of best overall response.

Tumor size was calculated as the sum of product diameters of the target lesions. Asterisks (\*) indicate patients who achieved uMRD ( $<10^{-4}$ ). Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; PV, pirtobrutinib and venetoclax; PVR, pirtobrutinib, venetoclax, and rituximab; uMRD, undetectable minimal residual disease

### Figure 2: Progression-free survival and overall survival rates.

Kaplan–Meier curves for progression-free survival (top panels) and overall survival (bottom panels) for patients treated with pirtobrutinib-based combination therapies. Tick marks indicate censored data.

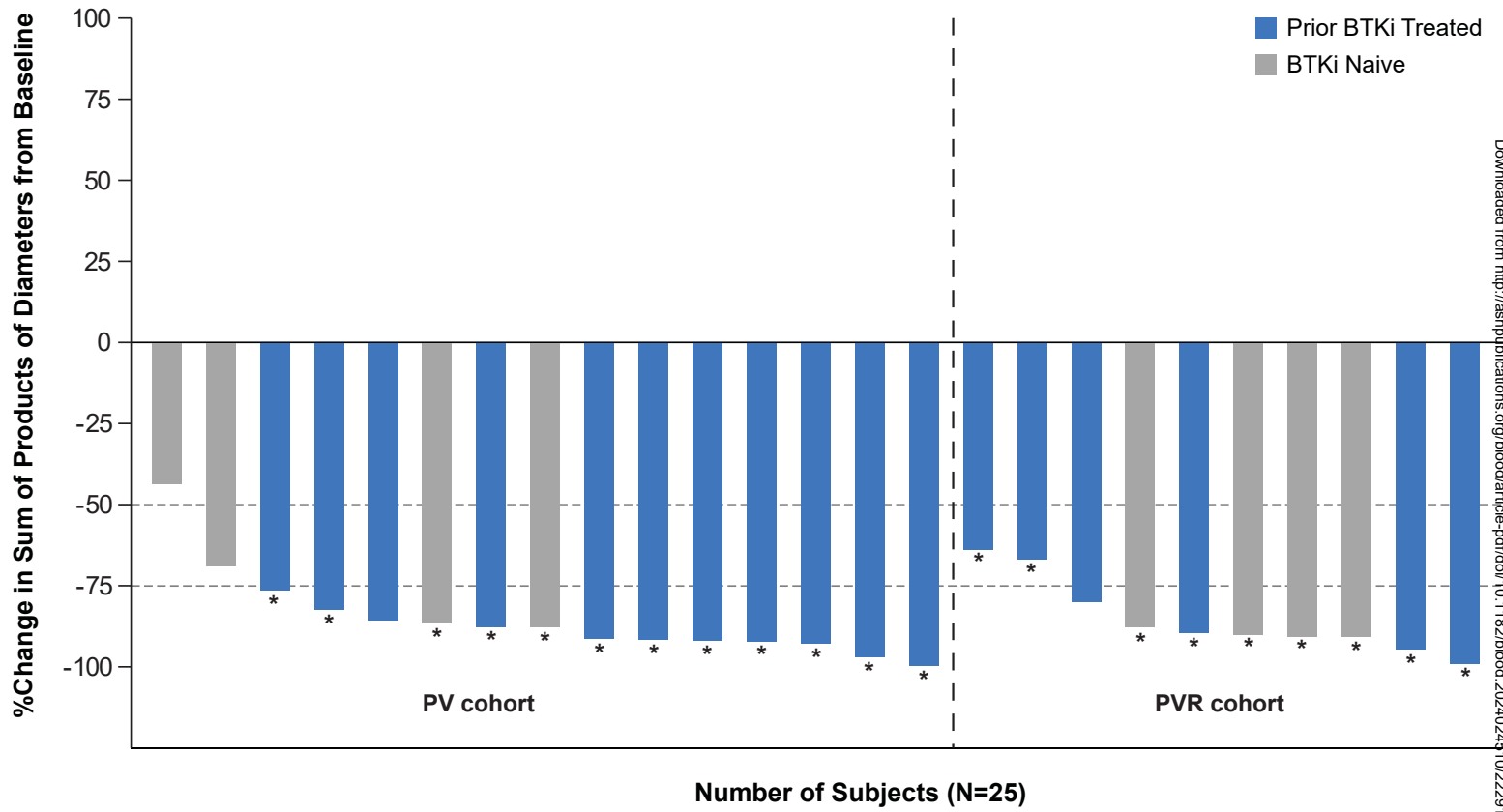
### Figure 3: Depth of MRD response in peripheral blood.

MRD was assessed by clonoSEQ assay (Adaptive Biotechnologies, Seattle WA) at screening and starting after cycle 3 day 1. (A-B) Sankey plots showing changes in MRD status at a sensitivity of  $<1$  CLL cell per 10000 nucleated cells ( $<10^{-4}$ ). (D-C) Line graphs showing MRD response for individual patients at a sensitivity of  $<1$  CLL cell per 1000000 nucleated cells ( $<10^{-6}$ ). MRD was assessed in 24 evaluable patients during 25 cycles of therapy. MRD data for one patient in the PV cohort is not shown because calibration did not identify a suitable dominant DNA sequence for MRD tracking. Study protocol required a lead-in cycle of pirtobrutinib monotherapy followed by 24 cycles of combination therapy with venetoclax, for a total of 25 cycles. Abbreviations: C, cycle; D, day; MRD, minimal residual disease; uMRD, undetectable minimal residual disease.

### Figure 4: Pirtobrutinib and venetoclax concentrations in patients treated with pirtobrutinib and venetoclax with or without rituximab.

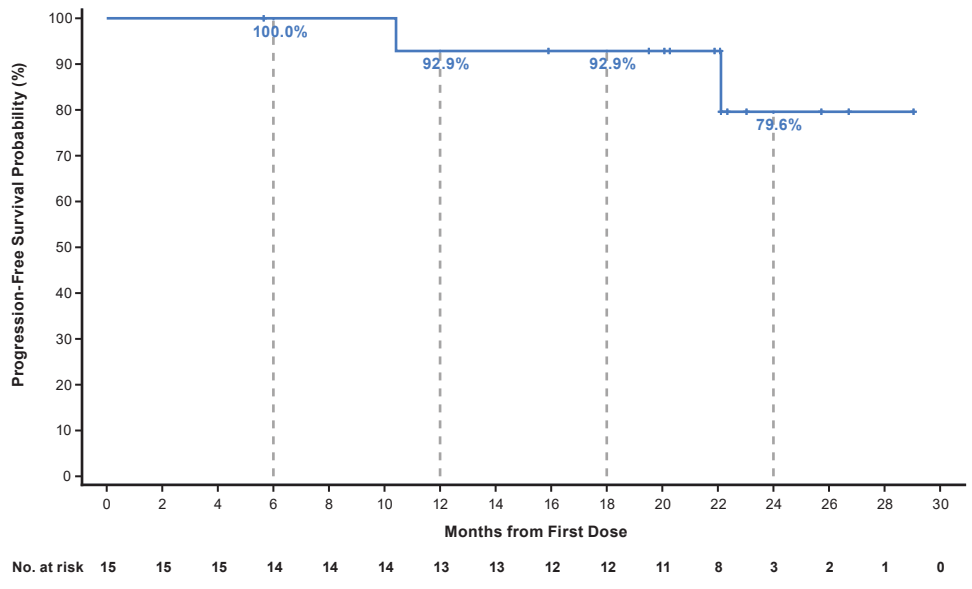
For pirtobrutinib concentrations, the open circles of cycle 1 day 8 represent pirtobrutinib alone, and closed symbols from cycle 2 and later represent pirtobrutinib with venetoclax.

# Figure 1

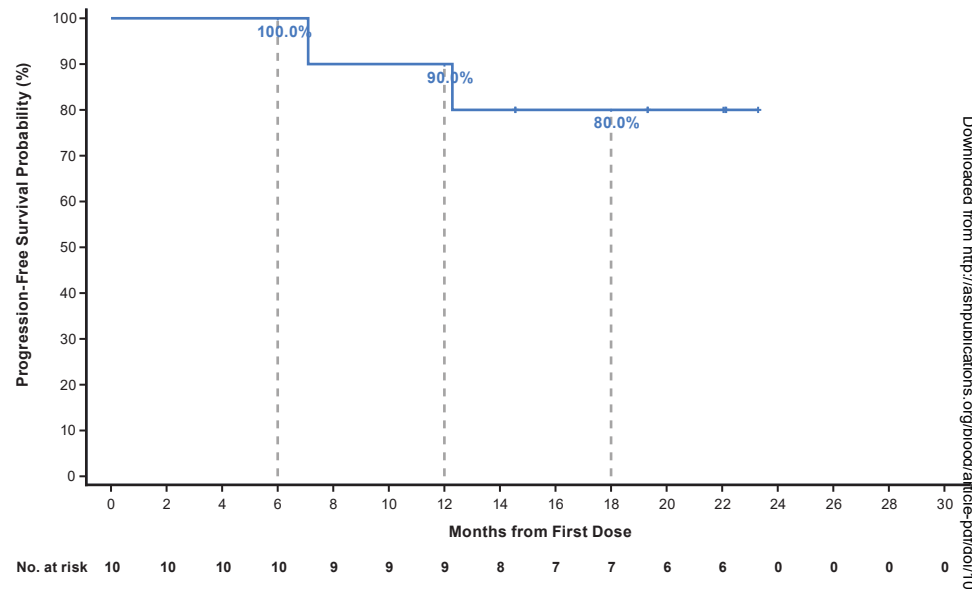


# Figure 2

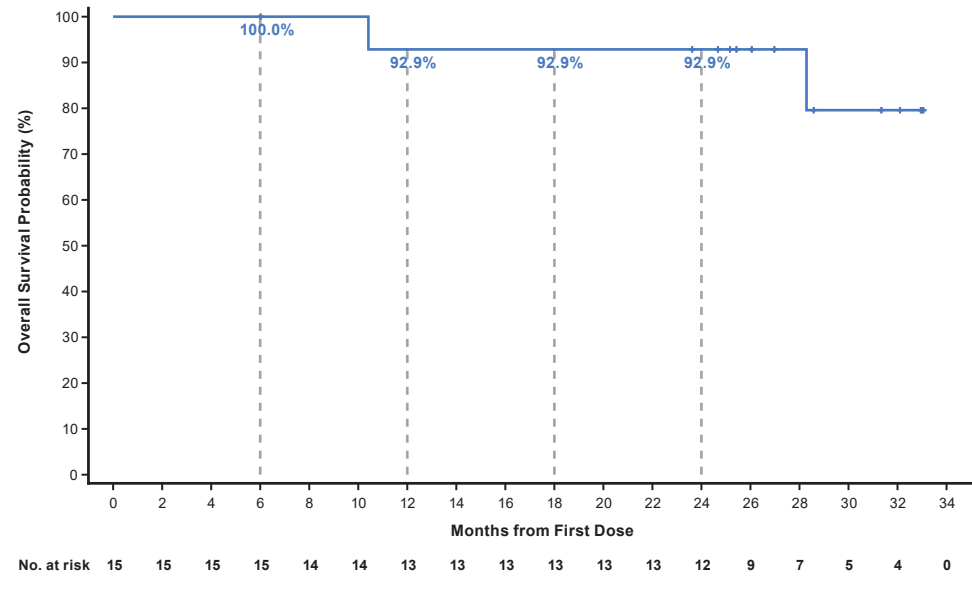
## A Pirtobrutinib and Venetoclax



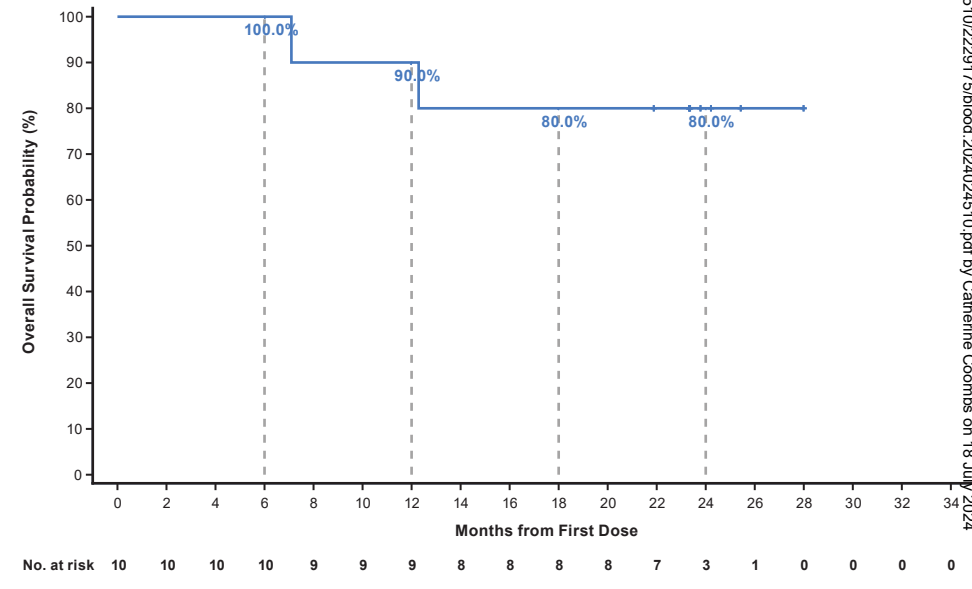
## B Pirtobrutinib, Venetoclax, and Rituximab



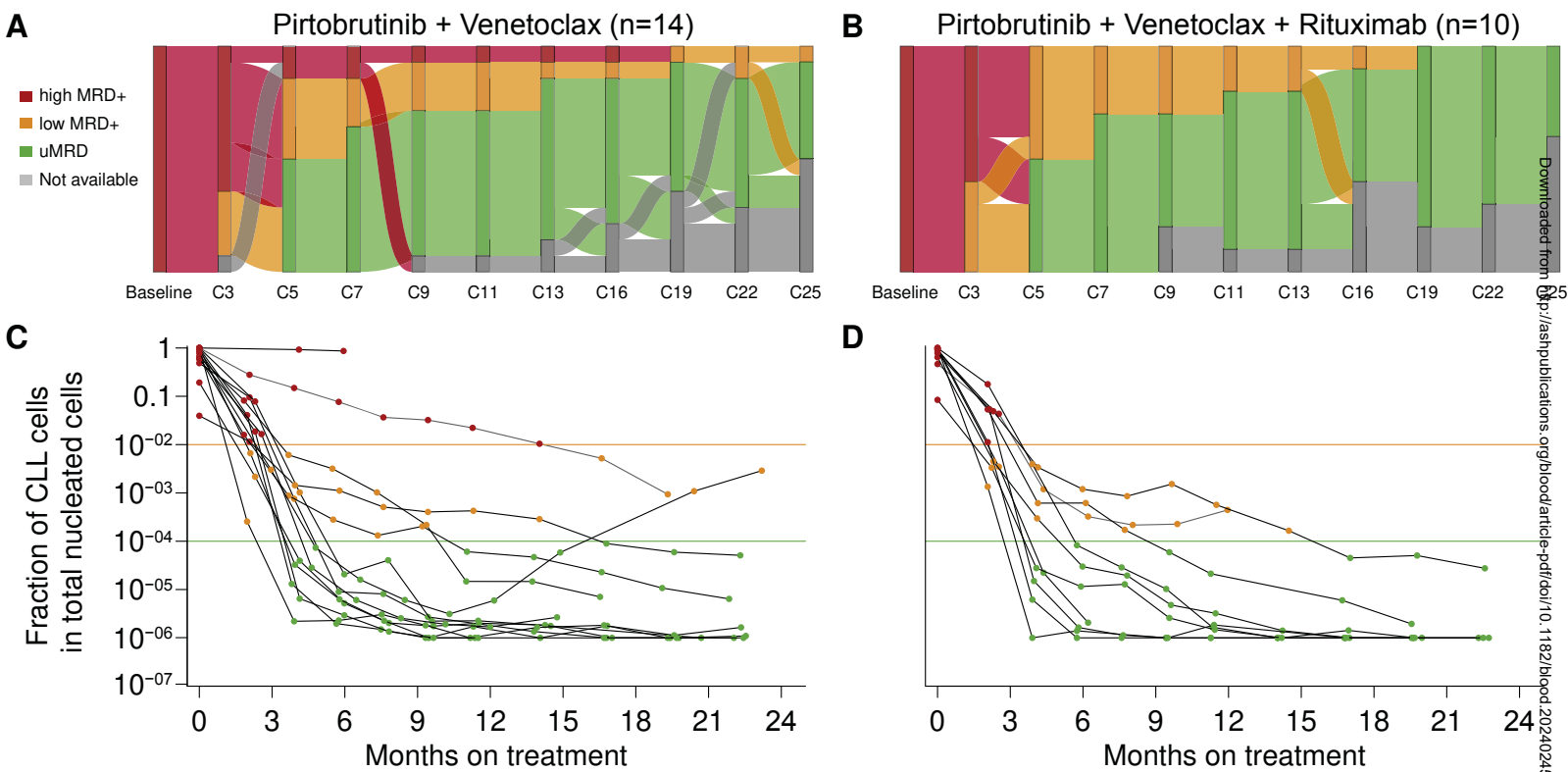
## C



## D



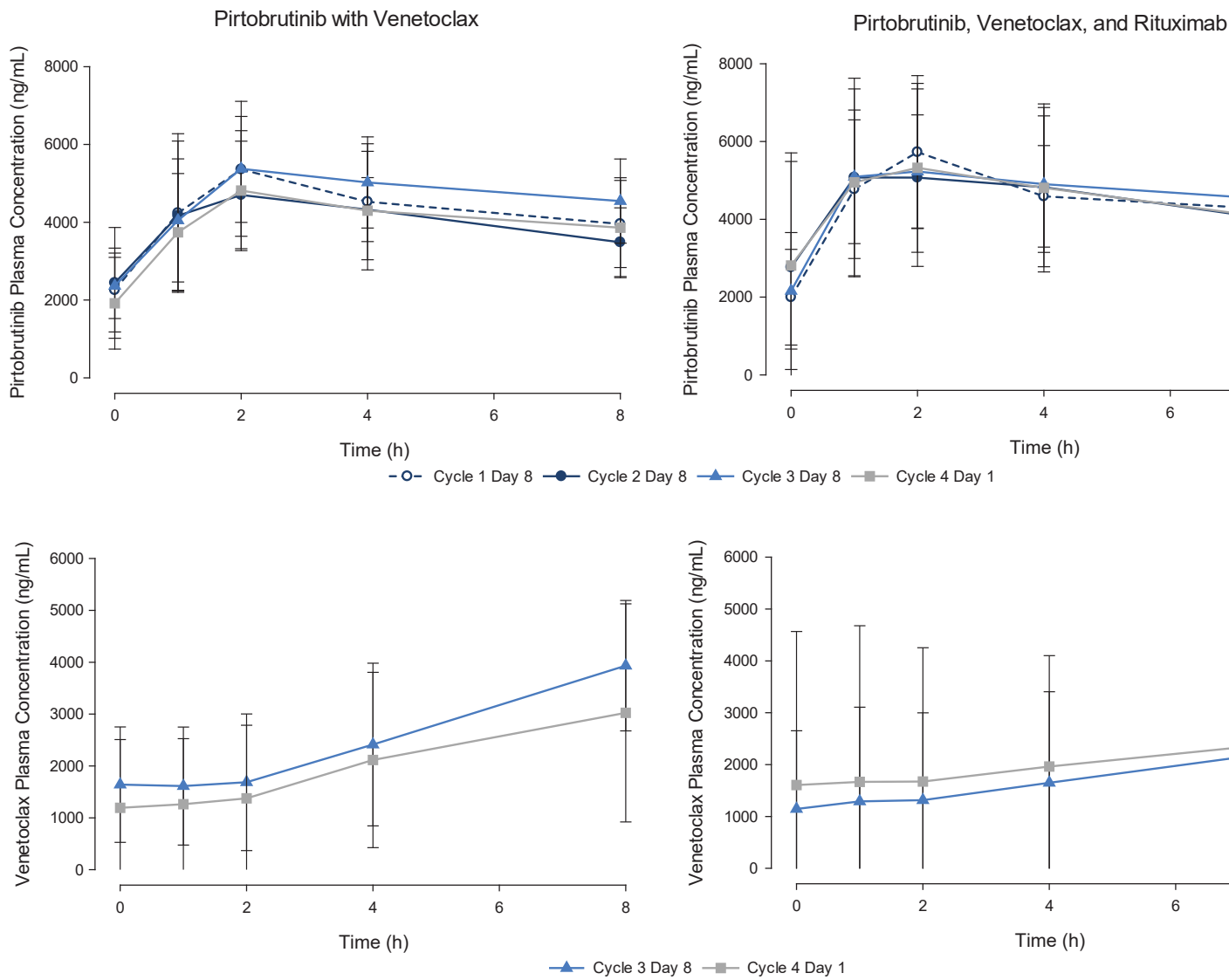
# Figure 3



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high MRD+, MRD  $\geq 10^{-2}$ ; low MRD+, between  $10^{-2}$  and  $10^{-4}$ ; uMRD, MRD  $< 10^{-4}$

# Figure 4



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# Fixed-Duration Pirtobrutinib Plus Venetoclax With or Without Rituximab in R/R Chronic Lymphocytic Leukemia (CLL): Phase 1b BRUIN Trial

## Background

Fixed-duration treatments with venetoclax and covalent Bruton tyrosine kinase inhibitors (cBTKi) have achieved deep remissions in patients with CLL.

Non-covalent (reversible) BTKi pirtobrutinib shows efficacy in patients with CLL, including those previously treated with cBTKi.

We tested fixed-duration pirtobrutinib plus venetoclax with or without rituximab (PV or PVR) in pretreated patients with CLL, including those who had received a cBTKi.

## Patients and methods

- ClinicalTrials.gov ID: NCT03740529
- Study design: Phase 1b clinical trial
- Participants: 25 adults with R/R CLL
  - PV (n=15)
  - PVR (n=10)
- Dosing regimen: Fixed duration, 25 cycles (1 cycle=28 days)
- Primary endpoint: Safety
- Secondary endpoints:
  - Overall response rate (ORR) including complete & partial response (CR; PR)
  - Undetectable minimal residual disease (uMRD)
  - Progression-free survival (PFS)
  - Duration of response (DOR)

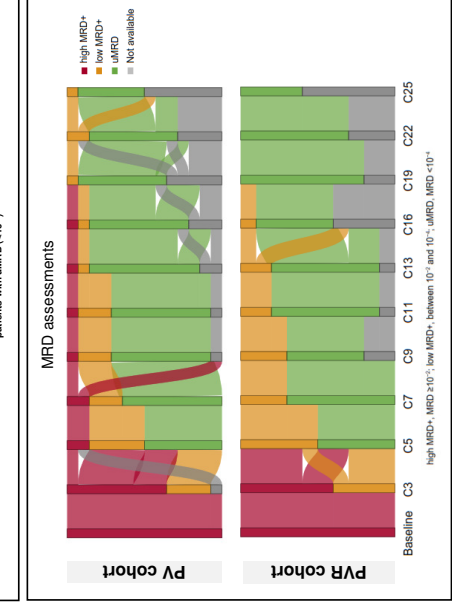
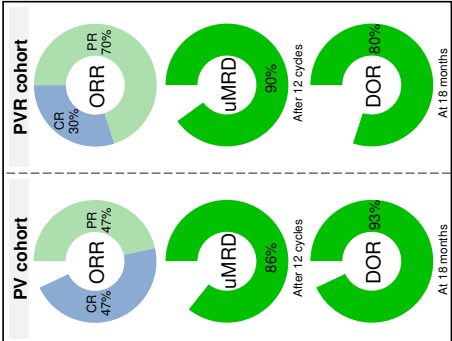
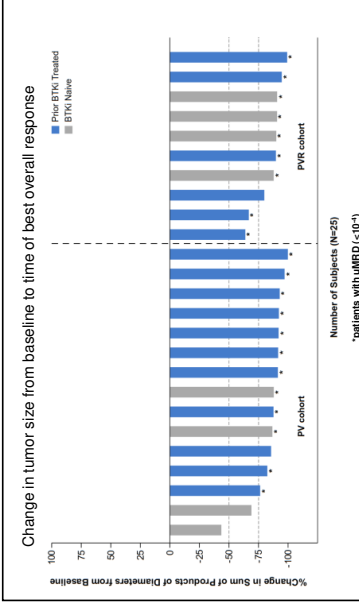
## Primary endpoint - both cohorts

- No dose-limiting toxicities
- Most common all-cause AEs: Neutropenia, diarrhea, fatigue, nausea
- Common grade ≥3 AEs:



- AE-related
  - Dose reduction (n=3/25)
  - Discontinuation (n=2/25)

## Secondary endpoints - per cohort



**Conclusions:** In both covalent BTK-naïve and BTK-exposed patients, fixed-duration PV and PVR regimens were well tolerated and demonstrated sufficiently encouraging efficacy to warrant further investigation in patients with R/R CLL.