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Long-term follow-up of venetoclax monotherapy in previously treated patients with Waldenström macroglobulinemia

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Abstract:
Venetoclax is highly active in previously treated Waldenström macroglobulinemia (WM). However, data on long-term durability and retreatment with venetoclax remain limited. Herein, we present an update of a prospective clinical trial of finite-duration venetoclax on 32 previously treated patients with WM. With a median follow-up of 81 months, twenty-three patients (72%) had disease progression, 17 (53%) began a new treatment, and 3 (9%) had died. The median progression-free survival (PFS) was 36 months, and the median treatment-free survival (TFS) was 43 months. PFS and TFS were superior in patients who attained at least a partial response to therapy. CXCR4 mutations or previous BTK inhibitor exposure did not impact these outcomes. Of the 17 patients who started a new therapy after completion of venetoclax therapy, nine were retreated with venetoclax alone or in combination (three attained a very good partial response, four a partial response, one had stable disease, and one did not respond). No BCL2 G101V mutations were detected in 52 CD19-selected bone marrow samples from 27 patients during treatment. Venetoclax induces durable responses in WM, allowing for retreatment in patients who progressed after completing therapy without the emergence of BCL2 G101V mutations. Clinical Trial Information: NCT02677324

Conflict of interest: COI declared - see note

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Agreement to Share Publication-Related Data and Data Sharing Statement: Deidentified data, study protocol, and informed consent form will be available immediately and up to 3 years from publication. Requests should be made via e-mail to jorgej_castillo@dfci.harvard.edu.

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Long-term follow-up venetoclax in Waldenström

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Abstract

Venetoclax is highly active in previously treated Waldenström macroglobulinemia (WM). However, data on long-term durability and retreatment with venetoclax remain limited. Herein, we present an update of a prospective clinical trial of finite-duration venetoclax on 32 previously treated patients with WM. With a median follow-up of 81 months, twenty-three patients (72%) had disease progression, 17 (53%) began a new treatment, and 3 (9%) had died. The median progression-free survival (PFS) was 36 months, and the median treatment-free survival (TFS) was 43 months. PFS and TFS were superior in patients who attained at least a partial response to therapy. *CXCR4* mutations or previous BTK inhibitor exposure did not impact these outcomes. Of the 17 patients who started a new therapy after completion of venetoclax therapy, nine were retreated with venetoclax alone or in combination (three attained a very good partial response, four a partial response, one had stable disease, and one did not respond). No *BCL2 G101V* mutations were detected in 52 CD19-selected bone marrow samples from 27 patients during treatment. Venetoclax induces durable responses in WM, allowing for retreatment in patients who progressed after completing therapy without the emergence of *BCL2 G101V* mutations. Clinical Trial Information: NCT02677324

Key Points

- Venetoclax provides durable responses in previously treated WM with a median PFS of 36 months. Superior PFS was seen when attaining ≥PR.

- *BCL2 G101V* mutations were not detected in patients who completed venetoclax therapy. Re-treatment with venetoclax induced deep responses.

Introduction

The B-cell lymphoma 2 (BCL2) antagonist venetoclax is safe and effective for patients with relapsed WM and is included as a treatment option in various guidelines, including the National Comprehensive Cancer Network. A multicenter, prospective phase II study in previously treated patients with WM treated with finite duration therapy with venetoclax monotherapy (50% had prior exposure to Bruton tyrosine kinase inhibitors) reported an overall response rate (ORR) of 84% and median progression-free survival (PFS) of 30 months[1].

However, the long-term durability of venetoclax therapy regarding PFS, treatment-free survival (TFS), overall survival (OS), the emergence of *BCL2* mutations, and the outcomes of venetoclax retreatment in patients with WM have not been described. The present report will provide insights into these issues.

Methods

The study design, methods, and results have been previously reported[1]. Briefly, participants were previously treated adults with a diagnosis of WM and an indication to treat based on the 2nd International Workshop for WM (IWWM-2) criteria[2,3]. Venetoclax was ramped up to a maximum dose of 800 mg orally once daily for two years. Tumor lysis syndrome (TLS) monitoring was mandatory during venetoclax ramp-up.

The study's primary objective was to achieve an ORR ≥70% (versus an alternative ORR ≤40%) with a double-sided alpha of 0.05 and a power of 80%. Categorical responses were assessed using modified IWWM-6 criteria[4]; extramedullary disease resolution was not required to attain a very good partial response (VGPR). Median follow-up time was estimated using the reverse Kaplan-Meier method. PFS was defined as the time between treatment initiation and disease progression, last follow-up, or death from any cause. TFS was defined as the time between treatment initiation and the next treatment, last follow-up, or death from any cause. OS was defined as the time between treatment initiation and the last follow-up or death from any cause.

All bone marrow samples underwent CD19-selection before genetic testing. Polymerase chain reaction (PCR) assays were used to detect *MYD88 L265P* and *BCL2 G101V* mutations. *CXCR4* mutational status was assessed using Sanger sequencing and allele-specific PCR.

Institutional review board approval and participants' written informed consent were obtained before research activities. The study followed the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Results

Table 1 shows baseline characteristics of 32 patients with WM who received at least one month of venetoclax monotherapy. As previously reported, the ORR was 84%, the

rate of partial response (PR) or better was 81%, and the VGPR rate was 19%. No additional long-term toxicities were observed beyond previously reported, with neutropenia (grade ≥2) being the most common, occurring in 53% of patients.

With a median follow-up of 81 months (95% CI 71-86), 23 patients (72%) had disease progression, 17 (53%) began a new treatment, and three (9%) had died. Of the three deaths, two were because of WM progression at 24 and 48 months, and one was of unknown cause at 54 months after treatment completion.

The median PFS was 36 months (95% CI 27-44) with a 5-year PFS rate of 24% (95% CI 10-41; **Figure 1A**). Participants who attained a PR or better had a longer median PFS of 42 months versus 7 months for those not achieving PR (p<0.001; **Figure 1B**). *CXCR4* mutational status (**Figure 1C**), VGPR attainment, time to response, and previous exposure to BTK inhibitors did not impact PFS (p>0.05 in all cases).

The median TFS was 43 months (95% CI 37-66) with a 5-year TFS rate of 39% (95% CI 20-57; **Figure 1D**). The median TFS was numerically longer in participants who attained a PR or better than in the patients who did not achieve PR (54 vs. 25 months; p=0.07; **Figure 1E**). *CXCR4* mutational status (**Figure 1F**), VGPR attainment, time to response, and previous exposure to BTK inhibitors did not impact TFS (p>0.05 in all cases).

The median OS was not reached, and the 5-year OS rate was 95% (95% CI 74-94).

As part of a dedicated subgroup analysis, we evaluated outcomes in patients with prior exposure to covalent BTK inhibitors. As reported in the initial trial publication, response rates tended to be lower in patients previously treated with a BTK inhibitor (ORR 75% vs. 93%; p=0.33) with a significantly longer time to response (4.5 vs.1.4 months; p<0.001). Prior BTK inhibitor exposure was not associated with significant differences in PFS (28 vs. 36 months; p=0.33) or TFS (42 vs. 54 months; p=0.90).

Of the 17 participants who began a new treatment, nine received retreatment with indefinite-duration venetoclax in a subsequent line of therapy. Six received venetoclax monotherapy (four attained a PR, one a VGPR, and one showed no response). Two patients received venetoclax with zanubrutinib (one attained VGPR, and one showed no response), and one received venetoclax with acalabrutinib (attained VGPR). All the patients underwent venetoclax ramp-up and TLS monitoring upon venetoclax reinitiation. Swimmer's plot depicting durability of response upon re-treatment is shown in **Figure 2**.

Of the eight patients who started a new treatment but did not receive venetoclax, four received BTK inhibitor monotherapy (three received ibrutinib and one zanubrutinib; all attained VGPR), and four received anti-CD20 monoclonal antibody combination therapy (two with bendamustine attaining VGPR and PR, and two with proteasome inhibitors without a response).

One event of histological transformation to diffuse large B-cell lymphoma (DLBCL) was observed two years into venetoclax retreatment in a patient without *CXCR4* mutations. The patient was treated with six cycles of polatuzumab vedotin, cyclophosphamide, doxorubicin, and prednisone and attained a complete response. Twenty-two months after the transformation event, the patient is alive without evidence of DLBCL.

Fifty-two bone marrow samples from 27 patients were available for *BCL2 G101V* mutation assessment, with more than one sample available in 17 patients. Nineteen samples were obtained at Cycle 6, sixteen at Cycle 12, one at Cycle 15, and sixteen at the end of treatment. *BCL2 G101V* mutations were not detected in any of the samples.

Discussion

In the present update, we provide insights into the long-term efficacy of venetoclax monotherapy in patients with relapsed WM. We observed a median PFS of 36 months and a median TFS of 43 months, with superior outcomes in patients attaining at least PR. We also observed that retreatment with venetoclax is reasonable in patients who did not have progressive disease while on venetoclax therapy. Notably, the initial course of fixed-duration venetoclax did not induce *BCL2 G101V* mutations, permitting retreatment.

This study included only patients with *MYD88 L265P* mutated disease, confirmed by highly sensitive CD19-selected bone marrow and allele-specific PCR testing[5], and

therefore supports venetoclax use in this population. Trialing venetoclax or repeating genotyping may still be reasonable in patients deemed *MYD88* wild-type by less sensitive methods. A recent retrospective study of WM patients treated with venetoclax off-trial reported a median PFS of 28.5 months with a median follow-up of 33 months; notably, 4 of 76 patients were MYD88 wild-type, although their outcomes were not analyzed separately[6].

The median PFS on venetoclax compares favorably to other treatment options in WM previously exposed to BTK inhibitors and chemoimmunotherapy. Specifically, the non-covalent BTK inhibitor pirtobrutinib, administered until disease progression or unacceptable toxicity, was associated with a median PFS of 20 months despite a high response rate[7]. However, the patient population in the pirtobrutinib study was more heavily pre-treated with a median number of therapies of three and 100% previous exposure to covalent BTK inhibitors. The single-arm, non-randomized nature of this trial, with a relatively small sample size, may have limited the power for subgroup analyses, precluding direct comparisons with alternative agents. As a result, cross-trial comparisons must be interpreted with caution. Given the evolving landscape of WM treatment with other agents under development, including the radioisotope iopofosine I-131[8], the antibody-drug conjugate loncastuximab tesirine[9], the bispecific antibody epcoritamab[10], the second-generation BCL2 antagonist sonrotoclax[11], and BTK degraders[12], the optimal positioning and sequencing of venetoclax remains unclear, but should be considered after covalent BTK inhibitor failure due to its comparatively lower

efficacy [13-16], or in patients in whom a BTK inhibitor is a less preferred approach, such as in patients with cardiac disease or bleeding diathesis.

Given the absence of comparative data, the decision to initiate venetoclax in the relapsed setting should be individualized, taking into account patient characteristics and preferences, including the desire for time-limited therapy with venetoclax versus continuous treatment with agents such as pirtobrutinib, or interest in participating in clinical trials. Patients with *CXCR4* mutations may benefit from venetoclax, as its activity appears unaffected by *CXCR4* status, in contrast to a numerically reduced response rate observed with pirtobrutinib in this subgroup [17]. Conversely, the slower response to venetoclax, particularly after prior covalent BTK inhibitor exposure, may favor pirtobrutinib in patients with high IgM transitioning from a BTKi, given its faster onset, lowering risk of rebound [18]. While specific data on the efficacy of venetoclax following pirtobrutinib or BTK degraders, or vice versa, are lacking, there is no biological rationale to suggest that prior therapy would preclude effectiveness, given the distinct mechanisms of action.

Early reports in patients with chronic lymphocytic leukemia (CLL) suggested venetoclax retreatment is reasonable for patients who progressed after completing fixed duration venetoclax and did not develop mutations in *BCL2*[19,20]. We report the first experience with venetoclax retreatment in WM patients. Like patients with CLL, venetoclax retreatment is not recommended in patients who have progressed on venetoclax therapy. Importantly, no *BCL2 G101V* mutations were detected in bone marrow samples

from patients up to the end of treatment, further supporting venetoclax retreatment. Still, the emergence of toxicities or other less common BCL2 resistance mechanisms (e.g., *D103Y*), which were not assessed in this study, should be considered when considering venetoclax retreatment [21].

The development of venetoclax in WM continues. We recently reported on a phase II study combining ibrutinib and venetoclax in previously untreated WM patients, which was stopped prematurely because of two grade 5 ventricular arrhythmias of unclear etiology[22]. Other studies evaluating venetoclax in the frontline setting include the combination of venetoclax plus rituximab versus ibrutinib plus rituximab (NCT04840602) and the combination of venetoclax and rituximab versus standard chemoimmunotherapy (NCT05099471). In the relapsed setting, a study combining pirtobrutinib and venetoclax is ongoing, with no arrhythmia events reported to date. Preliminary results show encouraging activity, with a VGPR rate of 56%, exceeding what has been reported with either agent alone. However, the long-term efficacy of this combination and the patient subgroups most likely to benefit remain to be determined [23].

In conclusion, despite the limitations associated with the small sample size of this prospective study, our study adds to the current body of evidence supporting the use of venetoclax in WM.

Authors contributions

JJC and SPT designed the study. JJC, JNA, TS, RHA, CAF, and SS provided the patients. KM, NB, JN, ARG, AG, and CJP provided administrative support. NT, CJP, and SPT performed the laboratory studies. JJC, AG, SPT, and SS performed the statistical analysis. JJC drafted the initial version of the manuscript. All the authors critically reviewed and approved the final manuscript.

Disclosures

JJC received honoraria from Abbvie, AstraZeneca, Beigene, Cellectar, J&J, Kite, Loxo, and Pharmacyclics, and research funds from Abbvie, AstraZeneca, Beigene, Cellectar, Loxo, and Pharmacyclics.

JNA received consulting fees from Abbvie, Adaptive Biotechnologies, ADC Therapeutics, AstraZeneca, Beigene, Genentech, Janssen, Lilly, Merck, NeoGenomics, and Pharmacyclics, and research funding from Beigene, Celgene/BMS, and Genentech,

TS received research funding from BMS and consulting fees from Abbvie, AstraZeneca, Beigene, BMS, and Gilead.

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SS received research funds or honoraria from ADC Therapeutics, Beigene, and Cellectar.

All other authors do not have conflicts of interest to disclose.

Data sharing statement

Deidentified data, study protocol, and informed consent form will be available immediately and up to 3 years from publication. Requests should be made via e-mail to jorgej_castillo@dfci.harvard.edu.

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Table 1. Selected baseline characteristics

Characteristic	**Participants (n=32)**
Median age at WM diagnosis, years (range)	58 (38-72)
Median age at venetoclax initiation, years (range)	66 (39-80)
Male sex (%)	18 (56)
Median serum IgM level, mg/dl (range)	3512 (642-7970)
Median hemoglobin level, g/dl (range)	10.6 (6.4-13.5)
Median platelet count, K/uL (range)	216 (60-445)
Serum beta-2-microglobulin level, mg/l (range)	3.6 (1.9-9.8)
Low IPSSWM score (%)	12 (38)
Intermediate IPSSWM score (%)	8 (25)
High IPSSWM score (%)	12 (38)
Median bone marrow involvement, % (range)	35 (4-90)
Adenopathy 1.5 cm or more (%)	9 (28)
Splenomegaly 15 cm or more (%)	8 (25)
MYD88 L265P mutation (%)	32 (100)
CXCR4 mutation (%)	17 (53)
Median number of prior therapies (range)	2 (1-10)
Previous anti-CD20 therapy (%)	28 (88)
Previous BTK inhibitor (%)	16 (50)

WM: Waldenstrom macroglobulinemia; IPSSWM: International Prognostic Scoring for WM; BTK: Bruton tyrosine kinase inhibitor

Figure legends

Figure 1. Kaplan-Meier estimates in 32 patients with Waldenstrom macroglobulinemia treated with venetoclax monotherapy. Progression-free survival for the entire cohort (A), and according to response depth (B), and *CXCR4* mutational status (C); and treatment-free survival for the entire cohort (D), and according to response depth (E), and *CXCR4* mutational status (F).

Figure 2. Swimmer's plot depicting durability of response in nine patients with WM who received venetoclax retreatment

Figure 1

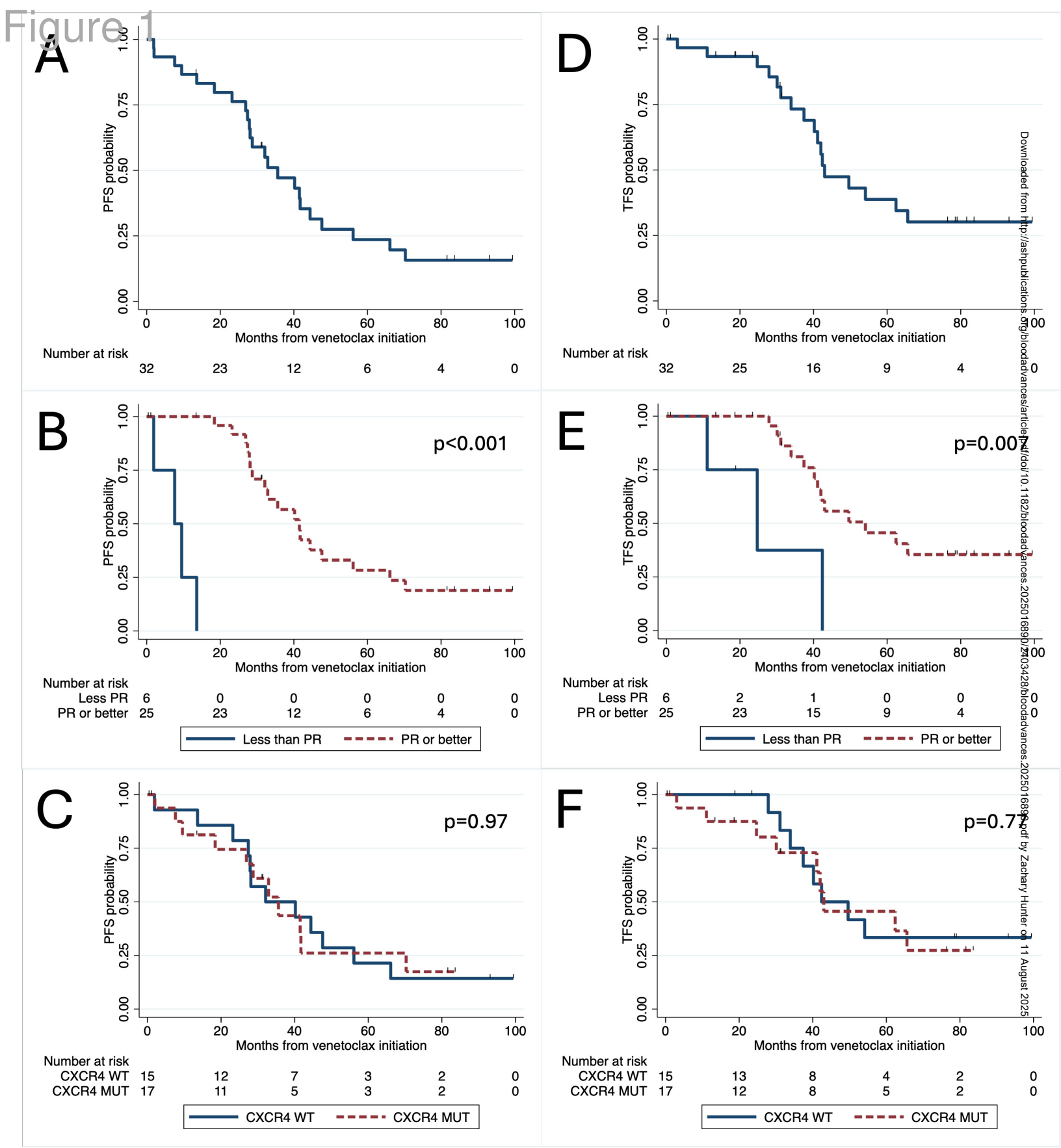

Figure 2