Outcomes in Patients with High-Risk Features after Fixed-Duration Ibrutinib plus Venetoclax: Phase II CAPTIVATE Study in First-Line Chronic Lymphocytic Leukemia

John N. Allan[1], Ian W. Flinn[2], Tanya Siddiqi[3], Paolo Ghia[4], Constantine S. Tam[5], Thomas J. Kipps[6], Paul M. Barr[7], Anna Elinder Camburn[8], Alessandra Tedeschi[9], Xavier C. Badoux[10], Ryan Jacobs[11], Bryone J. Kuss[12], Livio Trentin[13], Cathy Zhou[14], Anita Szoke[14], Christopher Abbazio[15], and William G. Wierda[16]

ABSTRACT

Purpose: The CAPTIVATE study investigated first-line ibrutinib plus venetoclax for chronic lymphocytic leukemia in 2 cohorts: minimal residual disease (MRD)-guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort). We report outcomes of fixed-duration ibrutinib plus venetoclax in patients with high-risk genomic features [del(17p), *TP53* mutation, and/or unmutated immunoglobulin heavy chain (IGHV)] in CAPTIVATE.

Patients and Methods: Patients received three cycles of ibrutinib 420 mg/day then 12 cycles of ibrutinib plus venetoclax (5-week ramp-up to 400 mg/day). FD cohort patients ($n = 159$) received no further treatment. Forty-three MRD cohort patients with confirmed undetectable MRD (uMRD) after 12 cycles of ibrutinib plus venetoclax received randomized placebo treatment.

Results: Of 195 patients with known status of genomic risk features at baseline, 129 (66%) had ≥1 high-risk feature. Overall response rates were >95% regardless of high-risk features. In patients with and without high-risk features, respectively, complete response (CR) rates were 61% and 53%; best uMRD rates: 88% and 70% (peripheral blood) and 72% and 61% (bone marrow); 36-month progression-free survival (PFS) rates: 88% and 92%. In subsets with del(17p)/*TP53* mutation ($n = 29$) and unmutated IGHV without del(17p)/*TP53* mutation ($n = 100$), respectively, CR rates were 52% and 64%; uMRD rates: 83% and 90% (peripheral blood) and 45% and 80% (bone marrow); 36-month PFS rates: 81% and 90%. Thirty-six–month overall survival (OS) rates were >95% regardless of high-risk features.

Conclusions: Deep, durable responses and sustained PFS seen with fixed-duration ibrutinib plus venetoclax are maintained in patients with high-risk genomic features, with similar PFS and OS to those without high-risk features.

See related commentary by Rogers, p. 2561

Introduction

Ibrutinib, a Bruton's tyrosine kinase inhibitor, and venetoclax, a BCL-2 inhibitor, are once-daily, oral-targeted therapies that are both approved for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL; refs. 1, 2). Through distinct and complementary mechanisms of action, the combination of ibrutinib and venetoclax has the potential to eradicate both dividing and resting CLL cells by preferentially targeting distinct cell compartments and CLL subpopulations (3–5). Ibrutinib mobilizes CLL cells out of lymph nodes and other protective lymphoid niches into peripheral blood, where they are more susceptible to venetoclax-induced apoptosis (5, 6). Ibrutinib also enhances the dependence of CLL cells on BCL-2, thereby increasing sensitivity to venetoclax and accelerating apoptosis (3, 6, 7). Synergistic antitumor activity with the combination of ibrutinib plus venetoclax has been demonstrated in preclinical models of CLL (8). The combination of ibrutinib plus venetoclax demonstrated high rates of undetectable minimal residual disease (uMRD) in both peripheral blood and bone marrow, high rates of progression-free survival (PFS), and durable treatment-free remissions in patients with previously untreated CLL/SLL treated with fixed-duration ibrutinib plus venetoclax in the CAPTIVATE and GLOW studies (9–11).

CLL is characterized by molecular heterogeneity resulting in variability in disease course, clonal growth rates, and response to treatment (12, 13). In particular, presence of *TP53* aberrations (deletion of the *TP53* gene locus on chromosome 17 [del(17p)] or mutations in the

[1]Weill Cornell Medicine, New York, New York. [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee. [3]City of Hope National Medical Center, Duarte, California. [4]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy. [5]Peter MacCallum Cancer Center and St. Vincent's Hospital and the University of Melbourne, Melbourne, Victoria, Australia. [6]UCSD Moores Cancer Center, San Diego, California. [7]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, New York. [8]North Shore Hospital/Waitematā District Health Board, Auckland, New Zealand. [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy. [10]Ministry of Health, Kogarah, New South Wales, Australia. [11]Levine Cancer Institute, Charlotte, North Carolina. [12]Flinders University and Medical Centre, Bedford Park, South Australia, Australia. [13]University of Padova, Padova, Italy. [14]Pharmacyclics LLC, an AbbVie Company, South San Francisco, California. [15]AbbVie, South San Francisco, California. [16]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas.

Note: Current address for C.S. Tam: Alfred Hospital and Monash University, Melbourne, Victoria, Australia.

Corresponding Author: John N. Allan, Weill Cornell Medicine, 407 East 61st Street New York, NY 10065. Phone: 646-962-2064; E-mail: joa9069@med.cornell.edu

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Translational Relevance

Results from the CAPTIVATE study demonstrated that first-line ibrutinib plus venetoclax provides deep, durable responses and sustained progression-free survival (PFS) in patients with chronic lymphocytic leukemia (CLL). The current analysis demonstrates that these clinical outcomes are maintained in patients with 1 or more high-risk genomic features known to confer inferior outcomes with chemoimmunotherapy, including del(17p), *TP53* mutation, or unmutated immunoglobulin heavy chain (IGHV), with PFS rates that were similar to patients without these high-risk features. These results support fixed-duration treatment with ibrutinib plus venetoclax as an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that provides clinically meaningful PFS and treatment-free remissions in the first-line treatment of patients with CLL, including those with del(17p), *TP53* mutation, or unmutated IGHV.

TP53 gene) is strongly prognostic for disease progression and worse overall survival (OS; refs. 13, 14), and patients with *TP53* aberrations experience inferior outcomes with first-line chemoimmunotherapy than patients without *TP53* aberrations (15–18). Mutational status of the variable region of the immunoglobulin heavy chain (IGHV) gene has also been identified as a prognostic factor in CLL, with poor prognosis in patients with unmutated IGHV (19, 20). Unmutated IGHV predicts inferior outcomes with first-line chemoimmunotherapy, whereas patients with mutated IGHV can achieve long-term PFS with chemoimmunotherapy (16–18, 21). Ibrutinib- and venetoclax-based regimens (including the fixed-duration regimen of venetoclax plus obinutuzumab) have both demonstrated PFS benefit over chemoimmunotherapy in patients with previously untreated CLL/SLL and high-risk genomic features, including del(17p), *TP53*, mutation, and/or unmutated IGHV (22, 23). In addition, combined ibrutinib plus venetoclax demonstrated promising efficacy in a phase II study in patients with previously untreated CLL with at least 1 high-risk feature [del(17p), *TP53* mutation, del(11q), or unmutated IGHV, or age ≥65 years; ref. 24].

The phase II CAPTIVATE study demonstrated deep and durable responses with ibrutinib plus venetoclax in first-line treatment of CLL/SLL (9, 10). Here, we report efficacy and safety of fixed-duration ibrutinib plus venetoclax in patients with high-risk genomic features [del(17p), *TP53* mutation, and/or unmutated IGHV] in the CAPTIVATE study.

Patients and Methods

Study design and treatment

Design of this trial was also summarized elsewhere (9, 10, 25). CAPTIVATE is a multicenter, international, phase II study comprising 2 sequentially enrolled cohorts: the MRD cohort (9) and the FD cohort (10). In both cohorts, patients received single-agent oral ibrutinib (420 mg once daily) lead-in for three 28-day cycles followed by 12 cycles of ibrutinib in combination with oral venetoclax [target dose 400 mg once daily after standard 5-week ramp-up, with tumor lysis syndrome (TLS) prophylaxis and monitoring per venetoclax prescribing information; ref. 2]. Subsequently, patients in the FD cohort received no further treatment regardless of MRD status at the end of treatment (10). Patients in the MRD cohort were randomly assigned to subsequent treatment according to MRD status after 12 cycles of ibrutinib plus venetoclax; the placebo arm comprised patients who achieved confirmed uMRD (defined as having uMRD $<10^{-4}$ by 8-color flow cytometry serially over at least three cycles, and undetectable MRD in both peripheral blood and bone marrow) and were randomly assigned to receive placebo in a double-blind manner (9).

Eligible patients were adults aged ≥18 to <70 years (MRD cohort) or ≤70 years (FD cohort) with previously untreated CLL/SLL requiring treatment per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (26), measurable nodal disease by computed tomography, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, and adequate hepatic, renal, and hematologic function. Patients with known allergy to xanthine oxidase inhibitors and/or rasburicase were excluded due to the requirement for TLS prophylaxis per venetoclax prescribing information (2).

The study was conducted in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and principles of the Declaration of Helsinki. The protocol was approved by the institutional review boards or independent ethics committees of all participating institutions. All patients provided written informed consent. This study is registered with ClinicalTrials.gov (NCT02910583).

Pooled analysis

In this exploratory *post hoc* analysis, data from the FD cohort and MRD cohort placebo arm were pooled for patients with known status for high-risk features [del(17p), *TP53* mutation, or unmutated IGHV] treated with fixed-duration ibrutinib plus venetoclax. Patients with unknown/missing status were excluded. Clinical outcomes of interest were overall response rate, defined as the proportion of patients with a best response of partial response (PR) or better by investigator assessment per 2008 iwCLL criteria (26, 27); complete response (CR) rate, including CR with incomplete bone marrow recovery (CRi); uMRD rates in peripheral blood and bone marrow ($<10^{-4}$ by 8-color flow cytometry); PFS by investigator assessment; OS; and safety. Adverse events (AE) were monitored during the treatment-emergent AE reporting period (from first dose until 30 days after the last dose of fixed-duration study treatment). Only serious AEs considered related to study treatment and secondary malignancies continued to be collected during follow-up posttreatment. PFS and OS were estimated using the Kaplan–Meier method. Outcomes were analyzed for subgroups with versus without ≥1 high-risk feature [del(17p), *TP53* mutation, and/or unmutated IGHV]. Analyses of outcomes by individual high-risk features were also performed for patients with or without del(17p)/*TP53* mutation, and for patients with unmutated IGHV or mutated IGHV. To address the potential bias from inclusion of patients from the MRD cohort placebo arm, all of whom achieved uMRD with ibrutinib plus venetoclax, sensitivity analyses were performed with patients from the FD cohort only (excluding patients from the MRD cohort placebo arm who were known to have uMRD at end of treatment). Given the exploratory *post hoc* nature of the analysis, no formal statistical comparisons were done; results are reported descriptively.

Cytogenetics were evaluated using FISH by local laboratory or by central laboratory; central laboratory results were used where available (93% of patients). Mutational status of *TP53* was assessed using next-generation sequencing by a central laboratory. The threshold for reporting *TP53* mutations was a variant allele frequency of ≥10% per European Research Initiative on CLL recommendations (28). IGHV gene mutational status was assessed with somatic hypermutation assay by a central laboratory. Karyotype was evaluated using CpG-

stimulated cytogenetics by a central laboratory; complex karyotype was defined as ≥3 abnormalities.

Data availability

Requests for access to individual participant data from clinical studies conducted by Pharmacyclics LLC, an AbbVie Company, can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Results

A total of 323 patients were enrolled in CAPTIVATE: 164 patients in the MRD cohort and 159 patients in the FD cohort. Overall, 202 patients were treated with fixed-duration ibrutinib plus venetoclax in the FD cohort ($n = 159$) and MRD cohort placebo arm ($n = 43$); baseline characteristics by cohort are described in Supplementary Table S1. Of 195 patients with known status of risk features at baseline, 129 (66%) patients had high-risk features, including 29 patients with del(17p)/*TP53* mutation and 119 patients with unmutated IGHV; 19 patients had both unmutated IGHV and del(17p)/*TP53* mutation. Baseline characteristics for patients with and without high-risk features are described in **Table 1**. At the time of analysis, median time on study was 38.9 months (range, 0.8–56.4) for patients with high-risk features, and 38.8 months (range, 2.6–53.4) for patients without high-risk features ($n = 66$). Median duration of posttreatment follow-up for the total pooled population was 25.1 months (range, 0.07–41.2).

Response rates

Overall response rates were >95% regardless of the presence of high-risk features (**Fig. 1**). CR/CRi rates were 61% [95% confidence interval (CI), 53–70] and 53% (95% CI, 41–65) in patients with and without high-risk features, respectively (**Fig. 1A**). Of patients who achieved CR/CRi, duration of CR/CRi lasting ≥12 cycles was confirmed in 92% (73/79) of patients with high-risk features and 97% (34/35) of patients without high-risk features. The 24-month landmark estimate for duration of CR/CRi was 93% (95% CI, 83–97) in patients with high-risk features and 100% (95% CI, 100–100) in those without high-risk features. In the subsets of patients with ($n = 29$) and without del(17p)/*TP53* mutation ($n = 169$), CR/CRi rates were 52% (95% CI, 34–70) and 60% (95% CI, 52–67), respectively (**Fig. 1B**). In the subsets of patients with unmutated IGHV ($n = 119$) and mutated IGHV ($n = 78$), CR/CRi rates were 61% (95% CI, 53–70) and 54% (95% CI, 43–65), respectively (**Fig. 1B**). The 24-month landmark estimate for duration of CR/CRi was 86% (95% CI, 54–96) and 97% (95% CI, 90–99) in patients with and without del (17p)/*TP53* mutation, respectively, and 94% (95% CI, 84–98) and 97% (95% CI, 83–100) in patients with unmutated IGHV and mutated IGHV, respectively. For patients with unmutated IGHV without del(17p)/*TP53* mutation ($n = 100$), the CR/CRi rate was 64% (95% CI, 55–73) and the 24-month landmark estimate for duration of CR/CRi was 95% (95% CI, 84–98).

Best uMRD rates were 88% (95% CI, 83–94) and 70% (95% CI, 59–81) in peripheral blood and 72% (95% CI, 64–80) and 61% (95% CI, 49–72) in bone marrow in patients with and without high-risk features, respectively (**Fig. 1C**). In patients who achieved CR/CRi, best uMRD rates were 96% and 83% in peripheral blood and 78% and 77% in bone marrow in patients with and without high-risk features, respectively. While uMRD rates were relatively consistent among patients with and without high-risk features, analysis of uMRD rates by individual high-risk features showed lower bone marrow uMRD rates in patients with

Table 1. Patient demographics and disease characteristics at baseline.

Characteristic	With high-risk features $n = 129$	Without high-risk features $n = 66$
Cohort, *n* (%)		
FD cohort	98 (76)	55 (83)
MRD cohort placebo arm	31 (24)	11 (17)
Age		
Median, years (range)	60 (33–70)	60 (35–71)
≥65 years, *n* (%)	34 (26)	19 (29)
Male, *n* (%)	85 (66)	43 (65)
ECOG PS, *n* (%)		
0	82 (64)	46 (70)
1	47 (36)	20 (30)
Histology, *n* (%)		
CLL	116 (90)	61 (92)
SLL	13 (10)	5 (8)
Rai stage, *n* (%)		
0/I/II[a]	92 (71)	46 (70)
III/IV	36 (28)	19 (29)
Missing	1 (1)	1 (2)
Bulky disease, *n* (%)		
≥5 cm	47 (36)	17 (26)
≥10 cm	6 (5)	0
ALC ≥25 × 10^9/L, *n* (%)	97 (75)	51 (77)
ALC, × 10^9/L		
Mean (SD)	89.5 (89.4)	84.0 (74.6)
Median (range)	67 (1–503)	53 (1–289)
Cytopenia at baseline, *n* (%)		
Any cytopenia	47 (36)	21 (32)
Hemoglobin ≤11 g/dL	40 (31)	11 (17)
Platelet count ≤100 × 10^9/L	10 (8)	11 (17)
ANC ≤1.5 × 10^9/L	10 (8)	7 (11)
Hierarchical cytogenetics classification, *n* (%)[b]		
Del(17p)	21 (16)	0
Del(11q)	33 (26)	3 (5)
Trisomy 12	18 (14)	12 (18)
Normal	28 (22)	13 (20)
Del(13q)	29 (22)	38 (58)
TP53 mutation, *n* (%)		
Yes	17 (13)	0
No	112 (87)	66 (100)
Del(17p) or *TP53* mutation, *n* (%)		
Yes	29 (22)	0
No	99 (77)	66 (100)
Unknown	1 (1)	0
IGHV gene mutation status, *n* (%)		
Unmutated	119 (92)	0
Mutated	10 (8)	66 (100)
Unknown	0	0
Complex karyotype, *n* (%)[c]		
Yes	27 (21)	7 (11)
No	82 (64)	52 (79)
Unknown	20 (16)	7 (11)

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count.

[a]Rai stage was 0 in 3/129 patients in the subgroup with high-risk features and 3/66 patients in the subgroup without high-risk features.

[b]Per Dohner hierarchy.

[c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

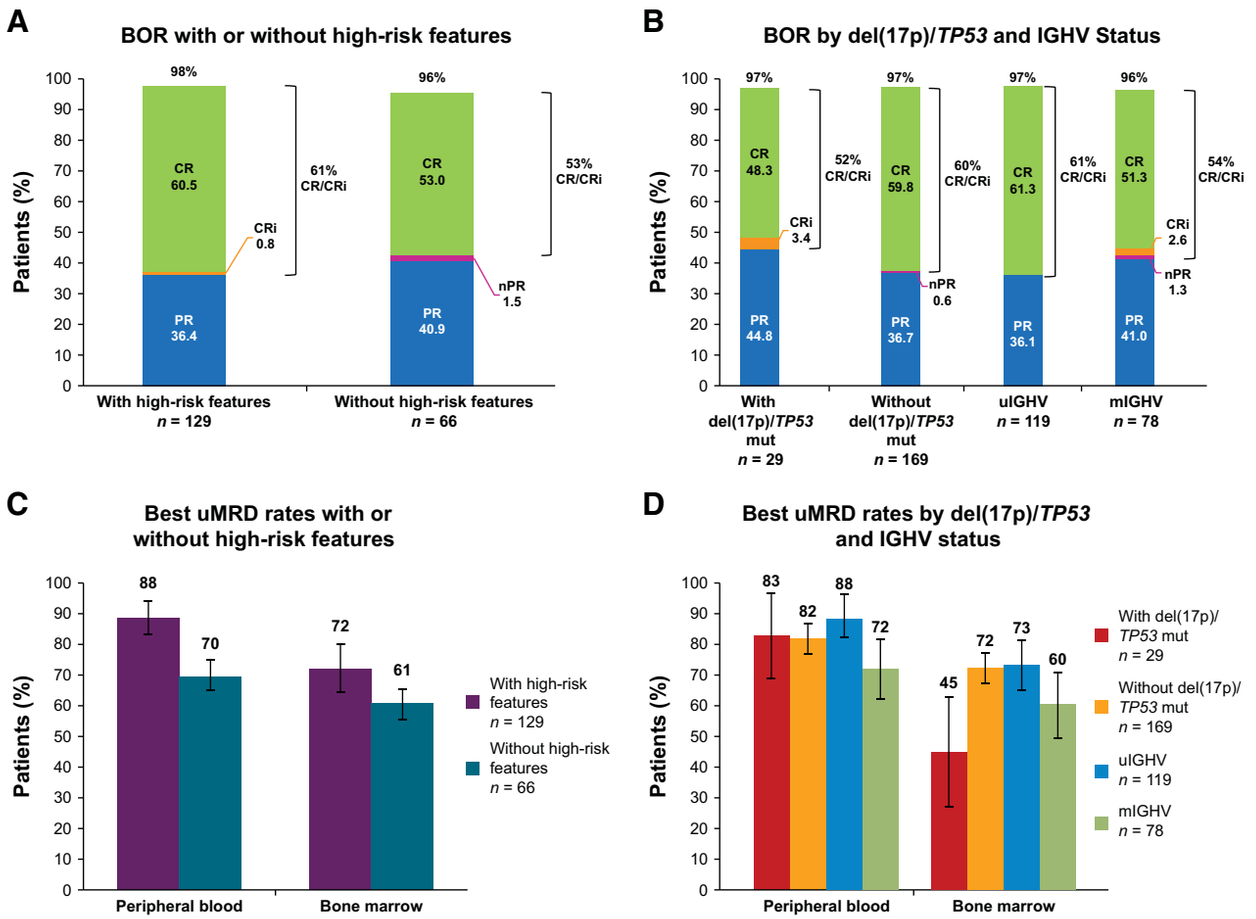

Figure 1.

Best overall response in patients with versus without high-risk features (**A**) and in the subsets of patients with or without del(17p)/*TP53* mutation and with unmutated IGHV or mutated IGHV (**B**). Best uMRD response[a] in patients with versus without high-risk features (**C**) and in the subsets of patients with or without del(17p)/*TP53* mutation and with unmutated IGHV or mutated IGHV (**D**). Error bars represent 95% CIs. [a]Patients with missing MRD status were considered to have detectable MRD. Abbreviations: BOR, best overall response; mIGHV, mutated IGHV; mut, mutation; nPR, nodular partial response; uIGHV, unmutated IGHV.

del(17p)/*TP53* mutation. Best uMRD rates in peripheral blood were 83% (95% CI, 69–97) and 82% (95% CI, 76–88) for the subsets of patients with and without del(17p)/*TP53* mutation, respectively, and 88% (95% CI, 82–94) and 72% (95% CI, 62–82) for the subsets with unmutated IGHV and mutated IGHV, respectively. Best uMRD rates in bone marrow were 45% (95% CI, 27–63) and 72% (95% CI, 65–79) for the subsets of patients with and without del(17p)/*TP53* mutation, respectively, and 73% (95% CI, 65–81) and 60% (95% CI, 49–71) for those with unmutated IGHV and mutated IGHV, respectively (**Fig. 1D**). In patients with unmutated IGHV without del(17p)/*TP53* mutation, best uMRD rates in peripheral blood and bone marrow were 90% (95% CI, 84–96) and 80% (95% CI, 72–88), respectively. In patients with CR/CRi, best uMRD rates in peripheral blood were 100% and 91% in the subsets of patients with and without del(17p)/*TP53* mutation, respectively, and 96% and 86% in the subsets of patients with unmutated IGHV and mutated IGHV, respectively; corresponding uMRD rates in bone marrow were 67% and 80% in patients with and without del(17p)/*TP53* mutation, respectively, and 78% and 79% in those with unmutated IGHV and mutated IGHV, respectively.

PFS and OS

PFS rates in patients with high-risk features were similar to those observed in patients without high-risk features, with 36-month PFS rates of 88% (95% CI, 81–93) and 92% (95% CI, 82–97), respectively (**Fig. 2A**). Compared with the relatively consistent PFS rates among patients with and without high-risk features, analysis of PFS by individual high-risk features showed a slightly lower PFS among the small subset of patients with del(17p)/*TP53* mutation. The 36-month PFS rates for the subsets of patients with and without del(17p)/*TP53* mutation were 81% (95% CI, 61–92) and 91% (95% CI, 85–94), respectively, and 36-month PFS rates for those with unmutated IGHV and mutated IGHV were 88% (95% CI, 80–93) and 92% (95% CI, 83–96), respectively (**Fig. 2B**). The 36-month PFS rate for patients with unmutated IGHV without del(17p)/*TP53* mutation was 90% (95% CI, 82–94). At 36 months, OS rates were >95% in patients with and without high-risk features (**Fig. 2C**) and in the subsets of patients with and without del(17p)/*TP53* mutation and with unmutated IGHV and mutated IGHV (**Fig. 2D**). The 36-month OS rate for patients with unmutated IGHV without del(17p)/*TP53* mutation was 98% (95% CI, 92–99). PFS and OS for the

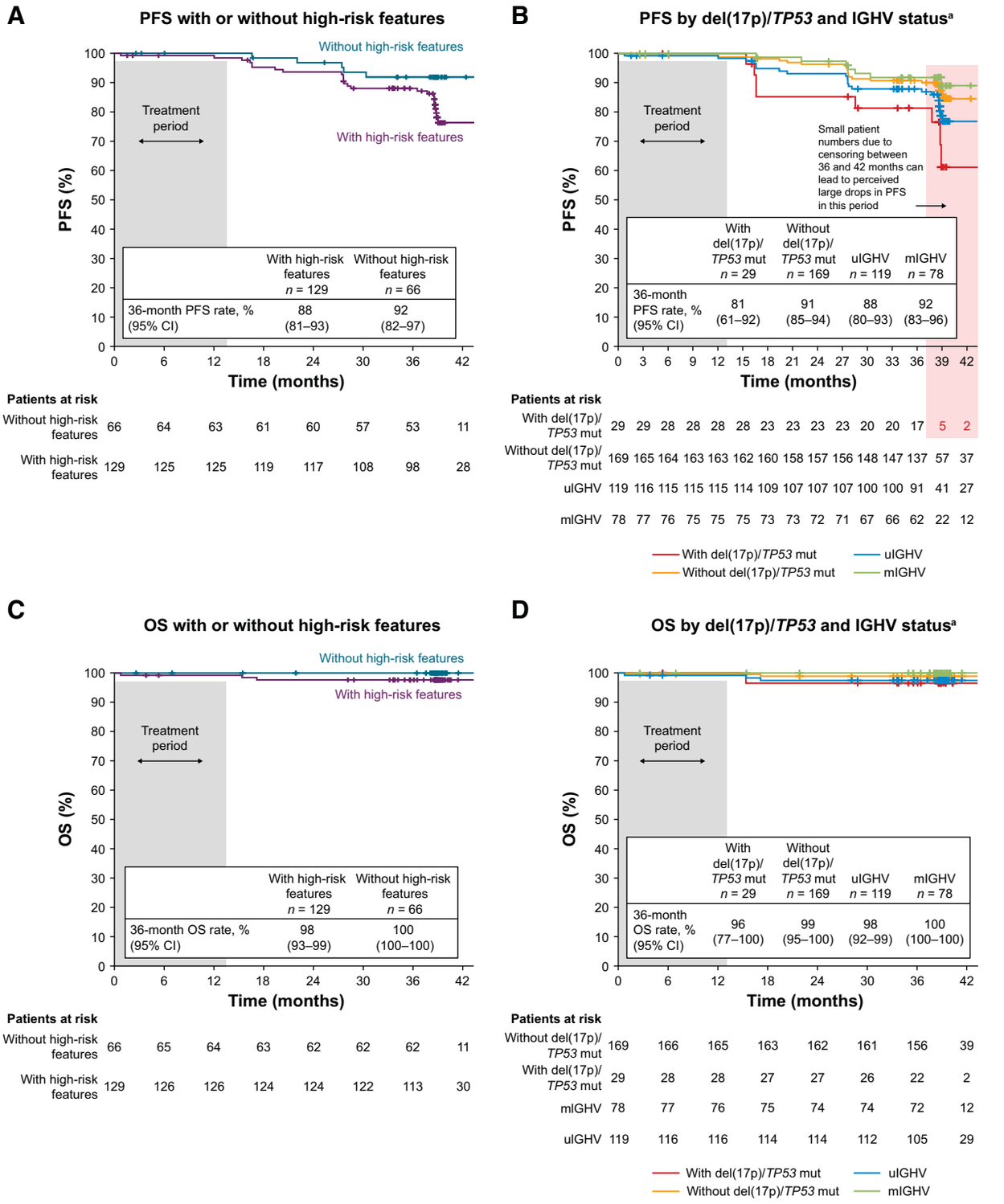

Figure 2.

Kaplan–Meier curves of PFS in patients with versus without high-risk features (**A**) and in the subsets of patients with or without del(17p)/*TP53* mutation and with unmutated IGHV or mutated IGHV (**B**). Kaplan–Meier curves of OS in patients with versus without high-risk features (**C**) and in the subsets of patients with or without del(17p)/*TP53* mutation and with unmutated IGHV or mutated IGHV (**D**). Tick marks indicate censored patients. [a]Due to many patients being censored between months 36 and 42 in the del(17p)/*TP53* mutation subset, PFS events among a small number of patients "at risk" beyond month 36 can lead to perceived large drops in PFS. Abbreviations: mIGHV, mutated IGHV; mut, mutation; uIGHV, unmutated IGHV.

total pooled population ($n = 202$) are shown in Supplementary Fig. S1.

Sensitivity analysis

Sensitivity analyses were performed to address the potential bias from inclusion of patients from the MRD cohort placebo arm, all of whom had uMRD at the end of treatment. Results of these sensitivity analyses including patients from the FD cohort only (excluding patients from the MRD cohort placebo arm) demonstrated similar outcomes to those observed in the total pooled population (Supplementary Table S2). Among patients from the FD cohort only, CR/CRi rates were 64% (95% CI, 55–74) in patients with high-risk features ($n = 98$) and 46% (95% CI, 32–59) in those without high-risk features ($n = 55$). At 36 months, PFS rates were 86% (95% CI, 77–92) and 90% (95% CI, 78–96) in patients with and without high-risk features, respectively, and OS rates were 97% (95% CI, 91–99) and 100% (95% CI, 100–100), respectively.

PD and retreatment

At the time of analysis, PD had occurred in 26 of 129 (20%) patients with high-risk features and in 5 of 66 (8%) patients without high-risk features. Among the 26 patients with high-risk features who had subsequent PD, best overall response with fixed-duration ibrutinib plus venetoclax was CR/CRi in 13 patients and PR in 13 patients; best MRD response was uMRD in peripheral blood in 23 patients and uMRD in bone marrow in 15 patients. Among the 5 patients without high-risk features who had subsequent PD, best overall response with fixed-duration ibrutinib plus venetoclax was PR in all 5 patients; none of these 5 patients achieved uMRD in peripheral blood or bone marrow. No resistance-associated mutations in *BTK*, *PLCγ2*, or *BCL-2* were detected at the time of PD in 26 patients with PD samples tested.

After experiencing PD, 9 patients with high-risk features and 3 patients without high-risk features have been retreated with single-agent ibrutinib. Of the 9 patients with high-risk features, 8 had unmutated IGHV, 2 had del(17p), 1 had *TP53* mutation, and 4 had complex karyotype at baseline. Of the 3 patients classified as without high-risk features, 2 had complex karyotype at baseline. In the patients with high-risk features retreated with single-agent ibrutinib [duration of retreatment, median 6.1 months (range, 0.03–27.6)], 6 of 6 patients with available response data achieved a best response of PR, and 3 additional patients are pending response evaluation. In the patients without high-risk features retreated with single-agent ibrutinib [duration of retreatment, median 3.7 months (range, 3.7–7.4)], 3 of 3 achieved a best response of PR.

Safety

At the time of analysis, no patients remained on fixed-duration treatment with ibrutinib plus venetoclax. Of the 129 patients with high-risk features, 121 (94%) completed planned treatment with ibrutinib and venetoclax. Of the 66 patients without high-risk features, 62 (94%) completed planned treatment with ibrutinib and venetoclax. Median treatment duration was 13.8 months (range, 0.7–24.9 months) for ibrutinib and 11.1 months (range, 9.9–22.1 months) for venetoclax in patients with high-risk features. Median duration of treatment was 13.8 months (range, 0.5–14.9) for ibrutinib and 11.1 months (range, 1.3–12.2) for venetoclax in patients without high-risk features.

The safety profile of ibrutinib plus venetoclax in patients with high-risk features was similar to that observed in patients without high-risk features (**Table 2**). The most common AEs of any grade during the treatment-emergent AE reporting period (from first dose until 30 days after the last dose of fixed-duration study treatment) were diarrhea (62% and 59% of patients with and without high-risk features, respectively), neutropenia (46% and 55%), nausea (42% and 44%), and arthralgia (33% and 32%). The most common grade 3/4 treatment-emergent AEs were neutropenia (36% and 36% of patients with and without high-risk features, respectively), and hypertension (9% and 3%). Overall, serious AEs during the treatment-emergent AE reporting period were reported in 22% and 21% of patients with and without high-risk features, respectively. During the fixed-duration treatment period, AEs led to discontinuation of ibrutinib only in 2% and 3% of patients with and without high-risk features, respectively, and discontinuation of both ibrutinib and venetoclax in 1% and 3% of patients, respectively.

Table 2. Treatment-emergent AEs[a] in patients with versus without high-risk features.

AEs, *n* (%)	With high-risk features *n* = 129	Without high-risk features *n* = 66
Most common AEs of any grade (occurring in ≥20% of patients)		
Diarrhea	80 (62)	39 (59)
Neutropenia[b]	59 (46)	36 (55)
Nausea	54 (42)	29 (44)
Arthralgia	43 (33)	21 (32)
Headache	33 (26)	19 (29)
Upper respiratory tract infection	32 (25)	20 (30)
Fatigue	30 (23)	22 (33)
Muscle spasms	29 (22)	21 (32)
Vomiting	23 (18)	15 (23)
Increased tendency to bruise	23 (18)	17 (26)
Most common grade 3/4 AEs (occurring in ≥5% of patients)		
Neutropenia[b]	47 (36)	24 (36)
Hypertension	12 (9)	2 (3)
AEs of clinical interest (any grade)		
Atrial fibrillation	8 (6)	2 (3)
Major hemorrhage[c]	2 (2)	1 (2)
Serious AEs	28 (22)	14 (21)
Related to study treatment	15 (12)	10 (15)
Fatal AEs	1 (1)[d]	0
AEs leading to discontinuation		
Ibrutinib only	3 (2)	2 (3)
Venetoclax only	0	0
Both ibrutinib and venetoclax	1 (1)	2 (3)
AEs leading to dose reduction		
Ibrutinib only	9 (7)	3 (5)
Venetoclax only	14 (11)	7 (11)
Both ibrutinib and venetoclax	3 (2)	4 (6)

[a]Includes AEs reported during the treatment-emergent AE period (from first dose until 30 days after the last dose of fixed-duration study treatment) and serious AEs considered related to study treatment and secondary malignancies occurring during posttreatment follow-up.
[b]Includes AEs reported using the preferred terms "neutropenia" or "neutrophil count decreased."
[c]Major hemorrhage was identified using the Standardised MedDRA Query for Hemorrhage, excluding laboratory terms.
[d]Sudden death in 1 patient during ibrutinib lead-in.

Discussion

Results from this pooled analysis of patients treated with fixed-duration ibrutinib plus venetoclax in the CAPTIVATE study confirm that deep, durable responses and sustained PFS seen with fixed-

duration ibrutinib plus venetoclax are maintained in patients with 1 or more high-risk genomic features [del(17p), *TP53* mutation, or unmutated IGHV], with PFS and OS rates that are similar to patients without high-risk features. The presence of high-risk genomic features did not appear to have a discernible impact on rates of treatment-emergent AEs, with a similar safety profile to that previously reported for the overall population of the CAPTIVATE FD cohort (10).

Interestingly, CR/CRi rates and uMRD rates were slightly higher in patients with 1 or more high-risk features than in patients without high-risk features, which may be at least partially due to the contribution of patients with unmutated IGHV who comprised 78% of the patients in the subgroup with high-risk features. In the primary analysis of the CAPTIVATE FD cohort, we observed that patients with unmutated IGHV had higher CR/CRi rates (62% vs. 47%) and higher uMRD rates in both peripheral blood (84% vs. 67%) and bone marrow (64% vs. 53%) than patients with mutated IGHV, which may reflect BCR pathway inhibition by ibrutinib (10). In the current analysis, the subset of patients with unmutated IGHV demonstrated high CR/CRi rates (61%) and uMRD rates in peripheral blood (88%) and bone marrow (73%). The small subset of patients with del(17p)/*TP53* mutation had similar rates of CR/CRi (52%) and uMRD in peripheral blood (83%) to those observed in patients without high-risk features (53% and 70%, respectively), whereas the rate of uMRD in bone marrow (45%) was markedly lower than that observed in patients without high-risk features (61%), albeit with a wide 95% CI.

Patients with CLL bearing *TP53* aberrations [del(17p) and/or *TP53* mutation] have poor outcomes on chemoimmunotherapy, with 3-year PFS and OS rates of only 18% and 38%, respectively, in those treated with first-line fludarabine, cyclophosphamide, and rituximab (FCR; ref. 16). In contrast, the 3-year PFS and OS rates were 81% and 96%, respectively, in patients with del(17p)/*TP53* mutation treated with fixed-duration ibrutinib plus venetoclax in the current study. These rates are consistent with those observed in patients with *TP53* aberrations with first-line continuous BTK inhibitor-based therapy while providing the advantage of fixed-duration therapy (29–31). While cross-trial comparisons should be interpreted with caution given differences in study designs and patient populations, when looking at other novel fixed-duration combinations, the 3-year PFS rate in this subgroup was 81% in the current analysis compared with the 3-year PFS rate of 60% achieved with fixed-duration venetoclax plus obinutuzumab in patients with del(17p)/*TP53* mutation in the CLL14 study (32). Similarly, patients with unmutated IGHV have worse outcomes on chemoimmunotherapy than patients with mutated IGHV, with 3-year PFS and OS rates of 55% and 86%, respectively, in patients with unmutated IGHV treated with first-line FCR (16). In the subset of patients with unmutated IGHV treated with fixed-duration ibrutinib plus venetoclax in the current study, 3-year PFS and OS rates were 88% and 98%, respectively. The 3-year PFS rate in patients with unmutated IGHV treated with fixed-duration venetoclax plus obinutuzumab in CLL14 was 81% (32), and 3-year PFS rates in patients with unmutated IGHV treated with time-limited venetoclax plus obinutuzumab and venetoclax plus obinutuzumab plus ibrutinib in the CLL13 study were 83% and 87%, respectively (33).

Our study has some limitations given the exploratory nature of these analyses. Inclusion of patients from the placebo arm of the MRD cohort had the potential to introduce bias because, by definition, all of these patients had confirmed uMRD after 12 cycles of ibrutinib plus venetoclax; however, sensitivity analyses excluding these patients demonstrated similar outcomes to those in the total pooled population. Although PFS appeared to be slightly worse in patients with del(17p)/*TP53* mutation in the current study, no meaningful statistical comparisons are possible given the relatively small number of patients with del(17p)/*TP53* mutation. Complex karyotype was not included in the definition of high-risk genomic features in the current analysis given the lack of consensus in the definition for complex karyotype (e.g., ≥3 or ≥5 abnormalities) and lack of clear guidance on how complex karyotype should inform decision making in the clinic (34). In addition, data on complex karyotype was missing in many patients (particularly in the FD cohort) and exclusion of these patients with missing data would have further reduced the numbers of patients in already small subgroups, whereas del(17p), *TP53* mutation, and IGHV mutation status were known for nearly all patients.

In conclusion, fixed-duration treatment with ibrutinib plus venetoclax demonstrated deep, durable responses in patients with 1 or more high-risk genomic features [del(17p), *TP53* mutation, or unmutated IGHV]. Patients with high-risk features had high PFS and OS rates that were similar to those observed in patients without high-risk features, although a slightly lower PFS rate was seen in the small subset of patients with *TP53* aberrations. Ibrutinib plus venetoclax had a manageable safety profile in patients with high-risk features, with 94% of these patients completing all planned treatment with ibrutinib plus venetoclax. These results support first-line treatment with ibrutinib plus venetoclax as an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that provides clinically meaningful PFS and treatment-free remissions in patients with CLL/SLL, including those with high-risk genomic features.

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Authors' Contributions

J.N. Allan: Conceptualization, resources, investigation, methodology, writing–review and editing. **I.W. Flinn:** Resources, investigation, writing–review and editing. **T. Siddiqi:** Resources, investigation, writing–review and editing. **P. Ghia:** Conceptualization, resources, investigation, methodology, writing–review and editing. **C.S. Tam:** Conceptualization, resources, investigation, methodology, writing–review and editing. **T.J. Kipps:** Resources, investigation, writing–review and editing. **P.M. Barr:** Conceptualization, resources, investigation, methodology. **A. Elinder Camburn:** Resources, investigation, writing–review and editing. **A. Tedeschi:** Resources, investigation, writing–review and editing. **X.C. Badoux:** Resources, investigation, writing–review and editing. **R. Jacobs:** Resources, investigation, writing–review and editing. **B.J. Kuss:** Resources, investigation, writing–review and editing. **L. Trentin:** Resources, investigation, writing–review and editing. **C. Zhou:** Conceptualization, data curation, formal analysis, validation, visualization, methodology, writing–review and editing. **A. Szoke:** Conceptualization, supervision, methodology, writing–review and editing. **C. Abbazio:** Conceptualization, visualization, methodology, writing–original draft, writing–review and editing. **W.G. Wierda:** Conceptualization, resources, investigation, methodology, writing–review and editing.

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Note

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