Parsaclisib, a PI3Kδ inhibitor, in relapsed and refractory follicular lymphoma (CITADEL-203): a phase 2 study

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Summary

Background Parsaclisib, a potent and highly selective PI3Kδ inhibitor, has shown clinical benefit in patients with relapsed or refractory (R/R) B-cell malignancies. This phase 2 study (CITADEL-203; NCT03126019, EudraCT 2017-001624-22) assessed efficacy and safety of parsaclisib monotherapy in patients with R/R follicular lymphoma (FL).

Methods Patients ≥18 years of age with histologically confirmed R/R FL (grade 1–3a) and prior treatment with ≥2 systemic therapies received parsaclisib 20 mg once daily (QD) for 8 weeks then parsaclisib 20 mg once weekly (weekly dosing group [WG]) or parsaclisib 20 mg QD for 8 weeks then parsaclisib 2.5 mg QD (daily dosing group [DG]); DG was selected for further assessment. Primary endpoint was objective response rate (ORR).

Findings At data cut-off (January 15, 2021), 126 patients had been treated (WG: n = 23; DG: n = 103). ORR (95% confidence interval [CI]) was 77.7% (68.4–85.3) with a complete response rate (95% CI) of 19.4% (12.3–28.4) in DG; median (95% CI) duration of response was 14.7 months (10.4–not estimable [NE]), median progression-free survival was 15.8 months (11.0–NE), and median overall survival was not reached. The most common any-grade treatment-emergent adverse events (TEAEs) among all treated patients included diarrhoea (n = 48, 38.1%), nausea (n = 31, 24.6%), and cough (n = 28, 22.2%); the most common grade ≥3 TEAEs were diarrhoea (n = 15, 11.9%), neutropenia (n = 13, 10.3%), and colitis (n = 7, 5.6%). Dose interruption, reduction, and discontinuation from TEAEs occurred in 46.8% (n = 59), 17.5% (n = 22), and 23.8% (n = 30) of patients, respectively.

Interpretation Treatment with parsaclisib demonstrated rapid and durable responses, and a manageable safety profile in patients with R/R FL.

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Keywords: Follicular lymphoma; Parsaclisib; PI3K inhibitor; Non-Hodgkin lymphoma

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Research in context

Evidence before this study

We search the PubMed database for articles on the use of PI3K inhibitors for the treatment of follicular lymphoma (FL) and identified 186 publications, of which 23 reported clinical trials in FL. The literature suggests targeting PI3K may be limited, due in part to class-specific toxicities including pneumonitis, rash, diarrhoea, opportunistic infections, and hepatotoxicity. Parsaclisib, a potent and highly selective PI3Kδ inhibitor that was structurally designed to improve safety associated with PI3K inhibitors, has demonstrated manageable safety and promising efficacy as monotherapy in patients with R/R indolent and aggressive B-cell NHL, including FL.

Added value of this study

CITADEL-203 is a phase 2, multicentre, open-label study that evaluated the efficacy and safety of parsaclisib in patients with R/R FL; the ORR was 78% in this population, which compares favourably to ORRs ranging from 42% to 59% achieved with other PI3K inhibitors. Common treatment-emergent adverse events (AEs) were diarrhoea, nausea, and cough, most of which were low grade and managed with dose interruption or reduction. Overall, results from CITADEL-203 demonstrate that parsaclisib produced rapid and durable responses and a manageable safety profile in patients with R/R FL.

Implications of all the available evidence

Data from this and other studies in marginal zone lymphoma (CITADEL-204) and mantle cell lymphoma (CITADEL-205) suggest parsaclisib could provide an effective treatment option for patients with R/R B-cell NHL, including FL. However, due to the inability to complete confirmatory studies or concerns over overall survival benefit in patients with indolent NHL or chronic lymphocytic leukaemia, several PI3K inhibitors have had indications or marketing authorisation withdrawn by the US Food and Drug Administration. Additional studies are required to address these concerns with PI3K inhibitors.

Introduction

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (NHL) and is generally incurable. Rituximab-containing chemotherapy with or without rituximab maintenance[1,2] is commonly used in the first-line setting; however, between 8% and 20% of patients relapse with aggressive disease and progress to death within 5 years.[3,4] For patients with relapsed or refractory (R/R) disease, treatment options include immunochemotherapy (such as rituximab-containing chemotherapy),[1,2] lenalidomide in combination with anti-CD20 agents,[1,5,6] immunomodulatory therapy such as chimeric antigen receptor T-cell therapy,[7–9] or targeted therapies.[10] Although the current therapy options have led to improvements in clinical outcomes, challenges still exist to improve efficacy and safety profiles. Several phosphoinositide 3-kinase (PI3K) inhibitors that had been approved for use as monotherapy in R/R FL by the US Food and Drug Administration (FDA) have recently been voluntarily withdrawn or had the R/R FL indication removed.[11–14] This was because of the inability to complete confirmatory studies in the required time period or the emerging safety concerns from confirmatory phase 3 combination studies.

The PI3K pathway plays a key role in B-cell receptor signalling, and overactivity of any of the four PI3K isoforms (α, β, δ, and γ) has been associated with B-cell malignancies including FL.[15–17] Monotherapy with PI3K inhibitors has demonstrated clinically meaningful efficacy for treatment of R/R NHLs. However, safety limitations stemming from both on- and off-target effects have restricted optimisation of efficacy outcomes.[17] Several adverse events (AEs) appear to be associated with the class (eg, transaminitis, diarrhoea, colitis, pneumonitis, neutropenia, and rash)[18–20]; other AEs, such as hyperglycaemia and hypertension, have been observed with PI3K inhibitors targeting the α isoform. Infections and autoimmune toxicities have also been observed upon inhibition of PI3Kδ and PI3Kγ due to alterations in lymphocyte signalling and biology.[17]

Parsaclisib is a potent and highly selective next-generation PI3Kδ inhibitor designed to improve safety while having strong inhibition of the δ isoform.[21,22] In biochemical assays, parsaclisib inhibited PI3Kδ activity (half maximal concentration = 1 nM) and was at least 10,000-fold more selective for PI3Kδ compared with PI3Kα, PI3Kβ, and PI3Kγ.[22,23] In the phase 1 CITADEL-101 study (NCT02018861), encouraging clinical outcomes with parsaclisib and improved safety were observed in patients with R/R NHL including FL.[21] Here, we report primary results from the CITADEL-203 study conducted to further evaluate the efficacy and safety of parsaclisib in patients with R/R FL.

Methods

Trial oversight

CITADEL-203 was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and all local ethical and legal requirements. The study protocol was approved by institutional review boards or independent ethics committees, and patients provided written informed consent before enrolment.

Study design

CITADEL-203 is a phase 2, multicentre, open-label study that planned to evaluate the efficacy and safety of parsaclisib in 120 patients diagnosed with R/R FL who had received at least two prior systemic therapies and were ineligible for haematopoietic stem cell therapy (Figure S1, appendix). The study protocol is available as a Supplemental appendix. The first 50 patients who met the eligibility criteria were planned to be allocated in a 1:1 ratio using a randomisation schedule through an interactive web response system into one of two groups —weekly dosing group [WG] or daily dosing group [DG]. Patients in the WG received oral parsaclisib 20 mg once daily (QD) for 8 weeks followed by 20 mg once weekly (QW); patients in the DG received oral parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD. An additional 70 patients were planned to be enrolled for further evaluation of safety and efficacy in the selected dosing group.

After preliminary evaluation of safety and efficacy from this study and other monotherapy studies in NHL, and data from pharmacokinetic studies (data not shown), the DG was selected for additional evaluation and all subsequent patients were enrolled in the DG. Patients in the WG were permitted to cross over to the DG or they could remain on their current regimen. Treatment for all patients continued until disease progression, death, unacceptable toxicity, or consent withdrawal. All patients were required to receive a standard *Pneumocystis jirovecii pneumonia* prophylaxis regimen while receiving parsaclisib and for 2–6 months after the last dose of parsaclisib.

Patients

Patients were at least 18 years of age with histologically confirmed R/R FL (grade 1, 2, or 3a); prior treatment with at least two prior systemic therapies and ineligible for haematopoietic stem cell therapy; radiographically measurable (computed tomography or magnetic resonance imaging) lymphadenopathy or extranodal lymphoid malignancy (defined as having at least one lesion that measures >1.5 cm in the longest transverse diameter and ≥1.0 cm in the longest perpendicular diameter); willing to provide a biopsy of lymph node or tissue; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; and adequate haematologic, hepatic, and renal function.

Key exclusion criteria included known histologic transformation from indolent NHL to diffuse large B-cell lymphoma; history of primary or metastatic central nervous system lymphoma; prior treatment with PI3K or Bruton's tyrosine kinase inhibitors (BTKi); receiving allogeneic or autologous stem cell transplantation, immunosuppressive therapy, anticancer or investigational drugs within protocol-defined intervals before the study; concurrent use of anticancer or potent CYP3A4 inhibitors or inducers; active graft versus host disease; history of stroke or intracranial haemorrhage within 6 months of the study; chronic or active infection requiring treatment (including human immunodeficiency virus, hepatitis B virus, and hepatitis C virus); or exposure to a live vaccine within 30 days of dosing.

Study endpoints and assessments

The primary study endpoint was independent review committee (IRC)–determined objective response rate (ORR) assessed by computed tomography or magnetic resonance imaging. Secondary endpoints included complete response (CR) rate, best percentage change in target lesion size from baseline (measured as the change in the sum of the product of target lesion diameters), duration of response (DOR), and progression-free survival (PFS), all determined by the IRC, and overall survival (OS; patients were contacted by the study site after the last dose of parsaclisib to assess survival status at least every 12 weeks until death, withdrawal of consent, or end of study, whichever occurred first), and safety and tolerability. Measurable disease and bone marrow examinations were performed at baseline to determine tumour status—if disease was present in the bone marrow at baseline, a bone marrow biopsy was required to confirm CR.

Safety was assessed by monitoring frequency, duration, and severity of AEs (severity measured by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03), as well as by physical examinations, vital signs, 12-lead electrocardiogram, ECOG PS, and clinical laboratory blood and urine measurements. AEs of special interest associated with PI3K inhibitors were followed as part of standard safety monitoring and included colitis, diarrhoea, exfoliative dermatitis, febrile neutropenia, rash, intestinal perforation, pneumonitis, pneumonia, and *Pneumocystis jirovecii*, cytomegalovirus, herpes simplex virus, and varicella zoster virus infections. Laboratory events of special interest included increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and decreased neutrophils.

Exploratory study endpoints included profile of blood biomarkers at baseline and on treatment associated with response, resistance, and safety of parsaclisib. Plasma samples were collected for pharmacokinetic and translational biomarker (ie, changes in protein analytes associated with immune function such as interleukin [IL]-10, B-cell activating factor, and B-cell attracting chemokine) analysis by liquid chromatography tandem mass spectrometry. Study assessments were performed at protocol-defined time points (Table S1, appendix).

Statistical analyses

A sample size of approximately 120 patients was selected for this study so that if the true ORR is 51% for patients in both treatment groups, there would be approximately 93% probability of observing the lower

bound of the 95% confidence interval (CI) of ORR ≥35%. All patients who received at least one dose of parsaclisib constituted the full analysis set (used for the summary of demographics, baseline characteristics, patient disposition, and analysis of all efficacy data) and the safety population (used for all safety analyses). Patients who received at least one dose of parsaclisib and provided at least one post-dose plasma sample formed the pharmacokinetic/pharmacodynamic-evaluable population.

The ORR and complete response rate (CRR) were estimated with 95% CIs, with the CIs calculated using the exact method of binomial distribution. Kaplan–Meier estimates of median DOR, PFS, and OS were provided with respective 95% CIs, with the CIs calculated using the generalisation of Brookmeyer and Crowley's method with log–log transformation.[24] Forest plots were created to assess variability in ORR between subgroups defined in the protocol. Waterfall plots were generated to summarize best percentage change from baseline in sum of target lesions. Differentially expressed analytes for exploratory biomarker analyses were determined by paired t-test, comparing values at week 4 and 16 to paired values at baseline. Changes were deemed significant at a false discovery rate p-value <0.05 and absolute fold change ≥1.5.

This was not a randomised study and no statistical comparisons between the two treatment groups were planned; descriptive summaries for continuous and categorical variables were reported. Patients who were initially assigned to the WG but switched to the DG before starting the 20-mg QW period were included in the DG for analyses, and those who switched after starting the 20-mg QW period were included in the WG for analyses. Unless otherwise stated, all efficacy data presented are determined by the IRC. Statistical analyses were performed using SAS® software (v9.4).

Role of the funding source

Study sponsor was involved in the design of the study, data collection, analysis and interpretation of data, and the development and decision to submit this manuscript for publication.

Results

Patient demographics and disposition

Between March 14, 2018, and the primary analysis data cut-off date of January 15, 2021, 126 patients were enrolled and treated with parsaclisib at 44 international study sites, including 23 patients in the WG and 103 patients in the DG. Eleven patients switched from WG to DG after starting the 20-mg QW period. For all treated patients, the median age was 67.5 years (range, 40–88), 55.6% (n = 70) of patients were male, and 89.7% (n = 113) were White. Ninety-four per cent (n = 118) of patients had an ECOG PS of 0 or 1, 77.8% (n = 98) had advanced disease (Ann Arbor Stage III–IV), and 70.6% (n = 89) had a Follicular Lymphoma International Prognostic Index (FLIPI) risk category of intermediate or high; median number of prior therapies was 2.0 (range, 1–8) and 49.2% (n = 62) of patients were refractory to their most recent prior therapy (Table 1).

At the primary analysis cut-off, 19 patients (82.6%) from the WG had discontinued treatment and four patients remained on treatment, and 68 patients (66.0%) from the DG had discontinued treatment and 35 patients remained on treatment; the primary reasons for treatment discontinuation in the WG and DG were progressive disease (56.5% [n = 13] and 32.0% [n = 33], respectively) and AEs (17.4% [n = 4] and 22.3% [n = 23], respectively) (Fig. 1; Table S2, appendix). Among all patients who discontinued study treatment, three (WG, n = 1; DG, n = 2) opted to stop parsaclisib therapy to undergo stem cell transplant. The median duration of parsaclisib treatment in the DG was 8.4 months (range, 0.8–27.2) and the median follow-up time was 17.6 months (range, 5.7–33.1) from the first dose to data cut-off date (Table S2, appendix).

Efficacy

At the data cut-off for the primary analysis, the ORR based on IRC assessment for patients in the DG was 78% (95% CI 68–85), with a CRR of 19% (95% CI 12–28) (Table 2). The ORR based on investigator assessment was 76% (95% CI 66–84) and the CRR was 10% (95% CI 5–17) in the DG. In a subgroup analysis of IRC-determined ORR based on patient baseline characteristics, response rates were generally consistent with the primary analysis in the respective overall population (Figure S2, appendix). Nine patients enrolled in the study had received prior lenalidomide therapy; ORR based on IRC assessment was 77.8% (95% CI 40.0–97.2) with a CRR of 22.2% (95% CI 2.8–60.0) in these patients.

In the DG, among all IRC-evaluable patients with baseline and at least one postbaseline assessment, 93.9% (93 of 99) had tumour regression and 87.1% (81 of 93) of whom achieved a >50% reduction in target lesion size from baseline (Fig. 2). The median percentage change from baseline in target lesion size as assessed by the IRC was –83.2% (range, –100% to 39.7%) in the DG.

The median time to response was 8.1 weeks in the DG, with 75.0% (60/80) of responders demonstrating an objective response by their first scheduled disease assessment (Fig. 3A). The median DOR was 14.7 months (range 10.4–not estimable) in the DG (Fig. 3B). Median PFS was 15.8 months (95% CI 11.0–not estimable) (Fig. 3C) and estimated 6- and 12-month PFS rates were 76.3% (95% CI 65.9–84.0) and 59.7% (95% CI 47.6–69.9), respectively. Median OS was not reached in the DG (nor in all treated patients) (Fig. 3D); the estimated 6- and 12-month OS rates were 97.0% (95%

CI 91.0–99.0) and 92.0% (95% CI 83.8–96.1), respectively. Time to response, DOR, PFS, and OS curves for the WG are presented in supplemental material (Figure S3, appendix).

Safety

The safety population included all patients who received at least one dose of parsaclisib (DG, n = 103; all treated patients, N = 126). Treatment-emergent adverse events (TEAEs) were reported in 123 patients (97.6%) overall and in 100 patients (97.1%) in the DG based on MedDRA preferred terms (Table 3 and Table S3, appendix). The most common TEAEs (occurring in ≥20% of the total population) were diarrhoea (overall 38.1% [n = 48]; DG 43.7% [n = 45]), nausea (overall 24.6% [n = 31]; DG 24.3% [n = 25]), and cough (overall 22.2% [n = 28]; DG 24.3% [n = 25]). TEAEs led to parsaclisib discontinuation in 30 patients (23.8%) overall and in 26 patients (25.2%) in the DG. In the total population, 59 (46.8%) and 22 (17.5%) patients required treatment interruption or dose reductions owing to TEAEs, and in the DG, 49 (47.6%) and 21 (20.4%) patients required treatment interruption or dose reductions, respectively. Treatment-related TEAEs were reported in 94 patients (74.6%) overall and in 78 patients (75.7%) in the DG. The most common treatment-related TEAEs were diarrhoea (overall 27.8% [n = 35]; DG 33.0% [n = 34]), nausea (overall 11.9% [n = 15]; DG 11.7% [n = 12]), and neutropenia (overall 11.9% [n = 15]; DG 12.6% [n = 13]).

Grade ≥3 TEAEs occurred in 74 patients (58.7%) in the total population and in 61 patients (59.2%) in the DG (Table 3). The most common grade ≥3 TEAEs (occurring in ≥5% of the total population) were diarrhoea (overall 11.9% [n = 15]; DG 13.6% [n = 14]), neutropenia (overall 10.3% [n = 13]; DG 10.7% [n = 11]), and colitis (overall 5.6% [n = 7]; DG 6.8% [n = 7]). For patients with grade ≥3 diarrhoea or colitis events, the median (range) time to onset of grade ≥3 diarrhoea was 5.0 (0.2–12.9) months and grade ≥3 colitis was 5.7 (1.9–11.1) months. Serious TEAEs occurred in 57 patients (45.2%) in the total population and 47 patients (45.6%) in the DG population. The most common serious TEAEs (occurring in ≥5% of patients in the total population) were colitis (6.3% [n = 8]) and diarrhoea (7.1% [n = 9]); all the serious TEAEs of colitis and diarrhoea occurred in the DG. There were two fatal TEAEs that occurred during the study, both of which were in the DG and considered treatment-related by the investigator (pneumonia and Stevens-Johnson syndrome in one patient each).

Of the AEs of special interest assessed, in addition to diarrhoea and colitis (presented above), rash occurred in 20 patients in the total population (15.9%; 14 patients in DG), pneumonia in six patients (4.8%; five patients in DG), cytomegalovirus infection in three patients (2.4%; all in DG), pneumonitis in three patients (2.4%; two patients in DG), exfoliative dermatitis in two patients (1.6%; both in the DG), febrile neutropenia in two patients (1.6%; both in the DG), and *Pneumocystis jirovecii* infection in one patient (0.8%; in the DG) (Table S4, appendix).

Select new or worsening haematologic and chemistry laboratory abnormalities are presented in Table 4 and Table S5 (appendix). The most common new or worsening haematology laboratory parameters for the total population included neutropenia (n = 59, 46.8%), anaemia (n = 41, 32.5%), and thrombocytopenia (n = 28, 22.2%). Any-grade or grade 3 increases (worst

Characteristic	Weekly dosing group[a] (n = 23)	Daily dosing group (n = 103)	All treated patients (N = 126)
Age, median (range), years	65.0 (45–84)	69.0 (40–88)	67.5 (40–88)
≥65 years, n (%)	12 (52.2)	64 (62.1)	76 (60.3)
Male, n (%)	12 (52.2)	58 (56.3)	70 (55.6)
Race, n (%)			
White	21 (91.3)	92 (89.3)	113 (89.7)
Black	1 (4.3)	6 (5.8)	7 (5.6)
Asian	0	1 (1.0)	1 (0.8)
Other	1 (4.3)	4 (3.9)	5 (4.0)
ECOG PS, n (%)			
0	14 (60.9)	68 (66.0)	82 (65.1)
1	7 (30.4)	29 (28.2)	36 (28.6)
2	2 (8.7)	6 (5.8)	8 (6.3)
Ann Arbor staging, n (%)			
I	1 (4.3)	5 (4.9)	6 (4.8)
II	3 (13.0)	16 (15.5)	19 (15.1)
III	8 (34.8)	26 (25.2)	34 (27.0)
IV	11 (47.8)	53 (51.5)	64 (50.8)
Missing	0	3 (2.9)	3 (2.4)
FLIPI risk category, n (%)			
Low (0 or 1)	3 (13.0)	19 (18.4)	22 (17.5)
Intermediate (2)	10 (43.5)	22 (21.4)	32 (25.4)
High (≥3)	7 (30.4)	50 (48.5)	57 (45.2)
Unknown	3 (13.0)	12 (11.7)	15 (11.9)
Time since diagnosis, median (range), years	6.0 (1.7–28.2)	5.9 (0.2–32.2)	6.0 (0.2–32.2)
Number of prior treatments, median (range)	3.0 (1–6)	2.0 (1–8)	2.0 (1–8)
Prior therapies, n (%)			
Anti-CD20 mAb	23 (100)	102 (99.0)	125 (99.2)
Alkylating agents	22 (95.7)	96 (93.2)	118 (93.7)
HSCT	6 (26.1)	17 (16.5)	23 (18.3)
Lenalidomide	4 (17.4)	5 (4.9)	9 (7.1)
Status to most recent prior therapy, n (%)			
Relapsed	8 (34.8)	44 (42.7)	52 (41.3)
Refractory	12 (52.2)	50 (48.5)	62 (49.2)
Unknown/missing	3 (13.0)	9 (8.8)	12 (9.5)

ECOG PS = Eastern Cooperative Oncology Group performance status. FLIPI=Follicular Lymphoma International Prognostic Index. HSCT = hematopoietic stem cell transplantation. mAb = monoclonal antibody. [a]Includes 11 patients who switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period.

Table 1: **Baseline demographics and clinical characteristics.**

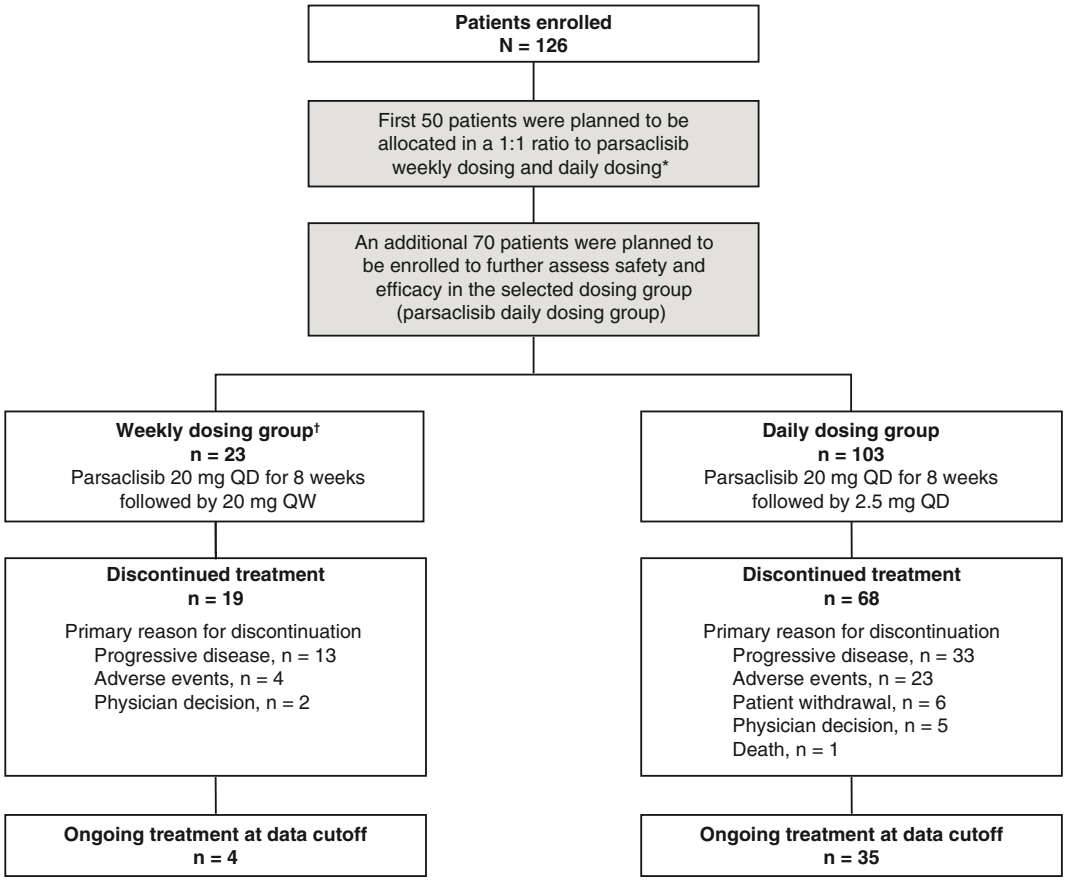

Fig. 1: CITADEL-203 patient disposition. QD = once-daily. QW = once-weekly. *Patients were allocated using a randomisation schedule to one of the parsaclisib dosing schedules, but this was not a randomised trial and no statistical comparisons were planned between treatment groups. †Includes 11 patients who switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period.

postbaseline increase) in ALT occurred among 30.2% (n = 38) and 1.6% (n = 2) of patients, and in AST occurred among 27.8% (n = 35) and 0% of patients, respectively. The only haematology laboratory parameter reported to have worsened to grade 4 postbaseline was neutrophil decrease (4.0% [n = 5] in all treated patients).

Response	Weekly dosing group[a] (n = 23)	Daily dosing group (n = 103)	All treated patients (N = 126)
Best overall response, n (%)			
Complete response	3 (13.0)	20 (19.4)	23 (18.3)
Partial response	12 (52.2)	60 (58.3)	72 (57.1)
Stable disease	6 (26.1)	13 (12.6)	19 (15.1)
Progressive disease	0	6 (5.8)	6 (4.8)
Not evaluable/assessed	2 (8.7)	4 (3.9)	6 (4.8)
ORR, % (95% CI)	65.2 (42.7–83.6)	77.7 (68.4–85.3)	75.4 (66.9–82.6)
CRR, % (95% CI)	13.0 (2.8–33.6)	19.4 (12.3–28.4)	18.3 (11.9–26.1)

CI = confidence interval. CRR = complete response rate. IRC = independent review committee. ORR = objective response rate. [a]Includes 11 patients who switched to 2.5 mg once-daily parsaclisib after starting the 20 mg once-weekly period.

Table 2: **Best overall response, and ORR and CRR among patients receiving parsaclisib by IRC review.**

Biomarker analysis

In the exploratory biomarker analysis, baseline and on-treatment serum samples were available for 108 patients. Serum proteomic analysis demonstrated that parsaclisib significantly ($p < 0.05$) reduced the expression of several cytokine, chemokine, and transmembrane receptors from baseline to week 4 post treatment, including CXCL13, FCER2, IL10, LTA/TNFB, TNFRSF4, TNFRSF9, and TNFRSF13B (Table S6, appendix). The significant reduction in these serum proteins was maintained at week 16 after transition to the 2.5-mg QD dose at week 8. A subset of serum proteins, including CXCL13 and IL10, rebounded toward baseline expression level at week 16 after transition to 20 mg QW in the WG (Figure S4, appendix).

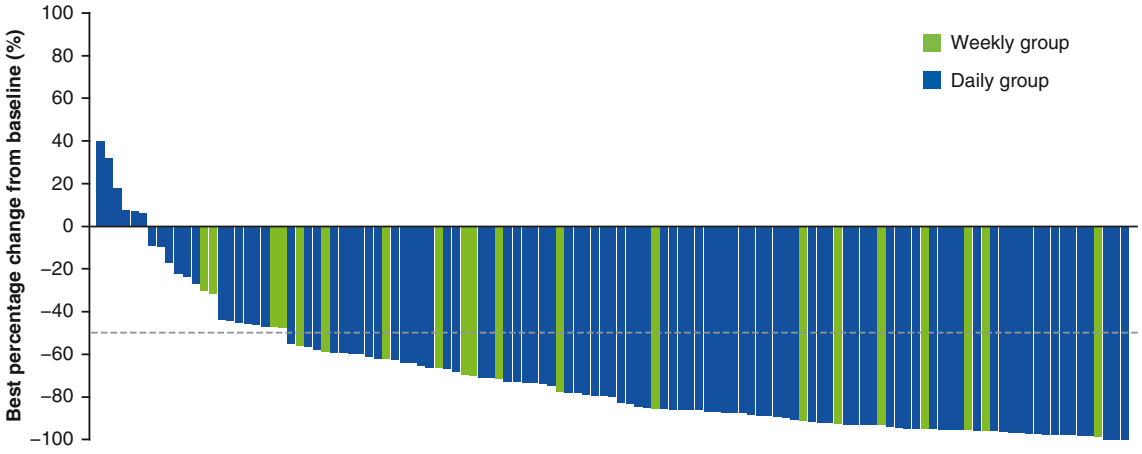

Fig. 2: Best percentage change from baseline in target lesion size by independent review committee.

Discussion

In this study, 126 patients with R/R FL who were BTKi-naive were treated with parsaclisib; of these, 103 patients received parsaclisib daily dosing (20 mg QD for 8 weeks followed by 2.5 mg QD [DG]) and 23 patients received weekly dosing (20 mg QD for 8 weeks followed by 20 mg QW [WG]). Continuous daily dosing of 20 mg parsaclisib has previously demonstrated prolonged responses in patients with aggressive or indolent NHL; however, discontinuation of treatment was common owing to AEs.[21] Based on pharmacokinetic modeling from the CITADEL-101 study, a single dose of parsaclisib 20 mg QW was expected to achieve maximal inhibition of the protein kinase B (AKT) pathway in excess of the

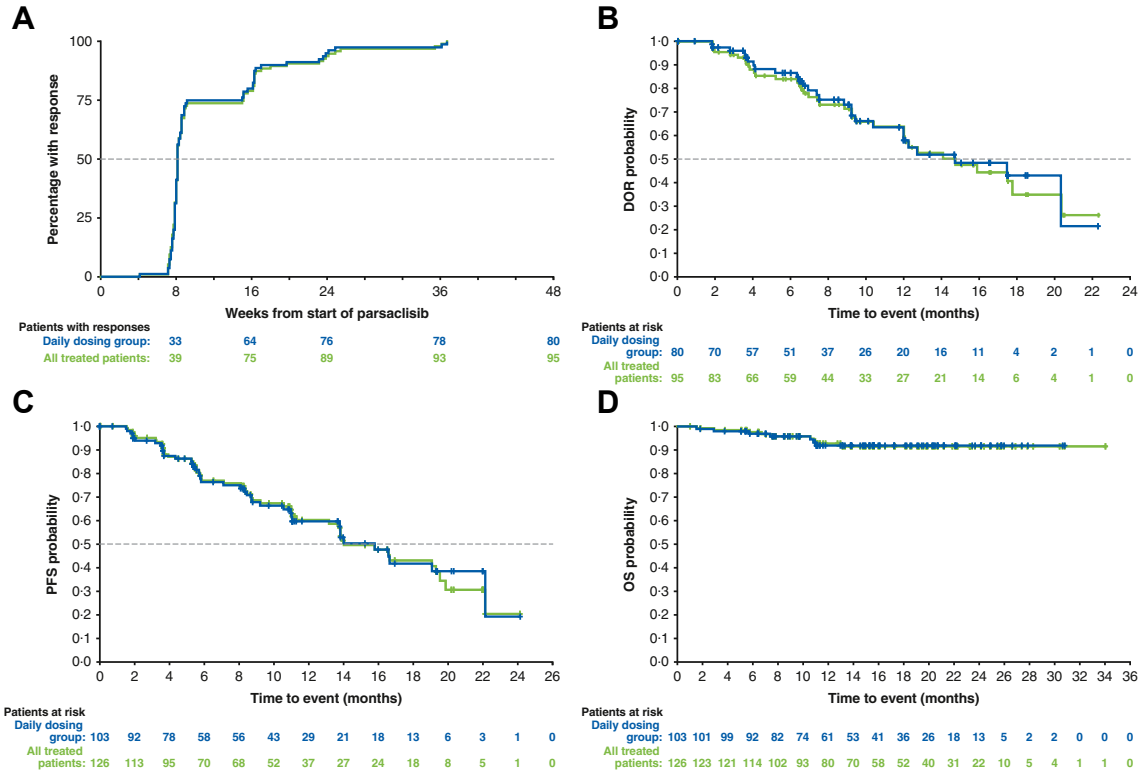

Fig. 3: (A) Cumulative time to response curves, and (B) Kaplan–Meier estimates of duration of response (DOR) and (C) progression-free survival (PFS) by independent review committee, and (D) overall survival (OS) in the daily dosing group (blue) and all treated patients (green).

Preferred term, n (%)	Daily dosing group (n = 103)		All treated patients (N = 126)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	100 (97.1)	61 (59.2)	123 (97.6)	74 (58.7)
Diarrhoea	45 (43.7)	14 (13.6)	48 (38.1)	15 (11.9)
Nausea	25 (24.3)	1 (1.0)	31 (24.6)	1 (0.8)
Cough	25 (24.3)	0	28 (22.2)	0
Fatigue	19 (18.4)	1 (1.0)	22 (17.5)	1 (0.8)
Pyrexia	20 (19.4)	3 (2.9)	22 (17.5)	3 (2.4)
Rash	14 (13.6)	3 (2.9)	20 (15.9)	4 (3.2)
Neutropenia	16 (15.5)	11 (10.7)	18 (14.3)	13 (10.3)
Asthenia	14 (13.6)	1 (1.0)	16 (12.7)	1 (0.8)
Arthralgia	11 (10.7)	0	13 (10.3)	0

TEAE = treatment-emergent adverse event.

Table 3: **Most common any-grade TEAEs (occurring in ≥10% of patients in the total population) and corresponding grade ≥3 TEAEs among patients receiving parsaclisib.**

concentration of the drug required for 90% inhibition (IC_{90}) for 36 h, but had no inhibition for approximately half of the dosing interval based on parsaclisib having a half-life between 8.6 and 11.5 h.[21] Comparatively, similar modeling data showed that a daily dosing of parsaclisib (2.5 mg QD) achieved a plasma concentration in excess of the half maximal inhibitory concentration (IC_{50}) for approximately 90% of a weekly dosing interval, indicating a less-maximal but more consistent inhibition of AKT, which was hypothesized to offer better clinical efficacy while reducing the severity and frequency of late-onset AEs during the maintenance phase. Following on the modeling data and evaluation of safety and efficacy from multiple studies investigating parsaclisib monotherapy in NHL, the DG was selected as the preferred maintenance dosing regimen for further enrolment and evaluation.

For the DG, the median age was 69.0 years and most patients had baseline ECOG PS of 0 or 1, which is generally representative of the R/R FL patient population. Most patients had grade 2 or grade 3a FL, had high-risk disease according to FLIPI score, had Ann Arbor Stage III or IV disease, and nearly half of the patients (48.5%) were refractory to their most recent prior therapy. Taken together, these disease characteristics are consistent with a high-risk population.

Preferred term, n (%)	Daily dosing group (n = 103)			All treated patients (N = 126)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutrophils decreased	49(47.6)	12 (11.7)	4 (3.9)	59 (46.8)	14 (11.1)	5 (4.0)
Haemoglobin decreased	35 (34.0)	3 (2.9)	NA	41 (32.5)	4 (3.2)	NA
Platelets decreased	23 (22.3)	0	0	28 (22.2)	0	0
ALT increased	31 (30.1)	2 (1.9)	0	38 (30.2)	2 (1.6)	0
AST increased	30 (29.1)	0	0	35 (27.8)	0	0

NA = Common Terminology Criteria for Adverse Events grade not applicable to the parameter. ALT = alanine aminotransferase. AST = aspartate aminotransferase. [a]Worst postbaseline grade reported for each patient.

Table 4: **Selected new or worsening haematologic and chemistry laboratory abnormalities.[a]**

The ORR for patients in the DG (Table 2) show 77.7% of patients achieved an objective response, including 19.4% who achieved a CR. The ORR by subgroup based on IRC assessment was generally consistent with the overall population. Activity of parsaclisib in FL was broad and deep with 93 out of 99 IRC-evaluable patients in the DG demonstrating a reduction from baseline in target lesions and 81 of them achieving a >50% reduction in target lesion size. The ORR observed is comparable with other PI3K inhibitors (idelalisib, 54%; duvelisib, 42%; copanlisib, 58.7%; umbralisib, 45.3%)[25–28] evaluated in similar patient populations (ie, patients with R/R FL who received at least two prior therapies, or at least one prior therapy for umbralisib). Notably, copanlisib and duvelisib inhibit additional isoforms of PI3K (copanlisib, PI3Kα; duvelisib, PI3Kγ) and umbralisib inhibits other targets (CK1ε). These results suggest that concomitant inhibition of these targets may not increase response rates relative to highly selective inhibition of PI3Kδ alone.

In the DG, the median time to response (8.1 weeks) was rapid, with 75% of the responses observed by the time of the first planned assessment (week 8). The median DOR (14.7 months) and median PFS (15.8 months) were both durable. Anecdotally, clinical utility of parsaclisib was further suggested by the objective responses observed in seven out of nine patients (ORR 77.8%) treated with either weekly or daily dosing who received prior lenalidomide combination regimens such as R2 (n = 8). Additionally, three patients who had clinical response stopped parsaclisib treatment to receive SCT having been ineligible for SCT at the start of the study.

The safety results observed in this study were consistent with known safety profiles of PI3K inhibitors, and no new safety concerns were identified.[18–20,28] Not unexpectedly, the most frequently reported TEAEs were AEs common to the PI3K inhibitor drug class (ie, diarrhoea, nausea, and cough), most of which were low-grade and manageable by dose interruptions or reductions. Grade 3 or higher TEAEs occurred in 58.7% of patients in the overall population; of interest, the most frequently experienced grade ≥3 TEAEs were diarrhoea, neutropenia, and colitis, having a median time to onset of 5.0, 2.8, and 5.7 months, respectively. In the overall population, 23.8% of patients discontinued treatment due to TEAE; diarrhoea and colitis were the most common TEAEs that led to treatment discontinuation. The median duration on study treatment was 8.4 months (0.8–27.2), which compares favourably to other PI3K inhibitors.

Parsaclisib was structurally designed to enhance specificity and reduce hepatotoxicity, with the goal of improving the safety profile associated with PI3Kδ inhibition.[23] The first approved PI3K inhibitor, idelalisib (selective for the PI3Kδ isoform) reported elevations in grade ≥3 ALT and AST (19% and 12%, respectively) in patients with indolent NHL.[19] In this study, laboratory

assessed ALT/AST elevations of grade ≥3 occurred in 1.6% and 0% of patients, respectively. No TEAEs of ALT or AST increases were reported to be serious or led to parsaclisib discontinuation. Another PI3K inhibitor, copanlisib, has also demonstrated low-grade ≥3 ALT/AST elevations. However, the inhibition of PI3Kα by copanlisib appears to induce α-specific toxicities of high-grade hyperglycaemia and hypertension.[28] As expected, lower rates of hyperglycaemia (all grade, 7.9%; grade ≥3, 1.6%) and hypertension (all grade, 7.1%; grade ≥3, 1.6%) were observed in patients treated with parsaclisib in the overall population compared with patients with indolent or aggressive NHL treated with copanlisib (hyperglycaemia: all grade, 50%; grade ≥3, 40.1%; hypertension: all grade, 29.6%, grade ≥3, 23.9%).[28]

Overall, parsaclisib has demonstrated meaningful, deep, and durable antitumour activity and a manageable safety profile that compares favourably with other PI3K inhibitors.[29,30] However, the FDA approval of one PI3K inhibitor, umbralisib, has been withdrawn, and the R/R FL indication has been removed for two PI3K inhibitors, idelalisib and duvelisib, owing to complications with confirmatory studies and safety concerns.[11–14] Due to the evolving PI3K inhibitor treatment landscape in NHLs, including these emerging safety signals associated with the PI3K inhibitors class and new approved therapies for R/R FL such as the CAR-T cell therapies axicabtagene ciloleucel and lisocabtagene maraleucel[7–9] and the targeted therapy tazemetostat,[10] further development of parsaclisib and other PI3K inhibitors would require extensive investigations, to address safety concerns and optimization of dosing strategies to mitigate long-term toxicities while demonstrating survival benefit over an extended period.

Contributors

All authors contributed to the acquisition, analysis, and interpretation of data, as well as to the drafting and critical review of the manuscript, and provided approval of the final version to be published. MT, RCL, FZ, DJD, WJ, and PJ directly accessed and verified the underlying data reported in the manuscript.

Data sharing statement

Incyte Corporation (Wilmington, DE, USA) is committed to data sharing that advances science and medicine while protecting patient privacy. Qualified external scientific researchers may request anonymised datasets owned by Incyte Corporation for the purpose of conducting legitimate scientific research. Researchers may request anonymised datasets from any interventional study (except phase 1 studies) for which the product and indication have been approved on or after January 1, 2020 in at least one major market (eg, United States, European Union, and Japan). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte Corporation's clinical trial data sharing policy and instructions for submitting clinical trial data requests are available at: https://www.incyte.com/Portals/0/Assets/Compliance%20and%20Transparency/clinical-trialdata-sharing.pdf?ver=2020-05-21-132838-960.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102130.

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