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ORIGINAL ARTICLE

Parsaclisib in Japanese patients with relapsed or refractory B-cell lymphoma (CITADEL-111): A phase Ib study

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Abstract

Parsaclisib, a potent, selective, next-generation PI3Kδ inhibitor, has shown clinical benefit in patients with relapsed or refractory B-cell lymphoma. We undertook a phase Ib study (CITADEL-111) evaluating safety, pharmacokinetics, and efficacy of parsaclisib in Japanese patients with relapsed or refractory B-cell malignancies. Patients received oral parsaclisib daily for 8 weeks then once weekly (10-mg dose, n = 3; 20-mg dose, n = 14). Pharmacokinetic samples were collected on days 1, 8, and 15, and efficacy was monitored according to Lugano criteria. At data cut-off (August 14, 2020), 6 patients (35.3%) remained on study treatment and 11 (64.7%) discontinued due to progressive disease (9 [52.9%]) or adverse events (2 [11.8%]). Median duration of treatment was 8.3 (range, 0.3–24.4) months. The most commonly reported nonhematologic adverse events were constipation (6 [35.3%]), nausea, and pyrexia (each 4 [23.5%]). Five patients (29.4%) experienced treatment-emergent new or worsening decreased neutrophils to grade 3 or 4. No treatment-emergent worsening in aminotransferase elevations to grade 3 or 4 were observed. Ten patients (58.8%) required dose interruption and 5 (29.4%) dose reduction. Body weight–normalized parsaclisib exposure was comparable between Japanese and Western patients. Objective response rate was 100% in follicular lymphoma (9 of 9 patients, including complete response in 2 patients [22.2%]) and marginal zone lymphoma (2 of 2 patients), and 16.7% in diffuse large B-cell lymphoma (1 of 6 patients). Results observed in Japanese patients with relapsed or refractory follicular or marginal zone lymphoma support further clinical development of parsaclisib in these patient populations.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCL, C-C motif chemokine ligand; CT, computed tomography; CXCL, B-cell attracting chemokine 1; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; FDG, fludeoxyglucose; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IL, interleukin; irAE, immune-related adverse event; MCL, mantle cell lymphoma; MMP, matrix metalloproteinase; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NCI, national cancer institute; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PET, positron emission tomography; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; QD, once daily; QW, once weekly; TEAE, treatment-emergent adverse event; TNFB, tumor necrosis factor-beta; TNFRSF, tumor necrosis factor receptor superfamily member.

Trial registration: NCT03314922; JapicCTI-184219.

KEYWORDS
B-cell lymphoma, Japan, non-Hodgkin lymphoma, parsaclisib, phosphatidylinositol 3-kinase

1 | INTRODUCTION

Non-Hodgkin lymphomas are lymphoproliferative malignancies that derive mostly from B cells (85–90%).[1] B-cell NHL subtypes are generally characterized by signaling pathway regulation (eg, B-cell receptor pathway activation in DLBCL, FL, MCL, and MZL).[2-4] B-cell receptor stimulation activates complex molecular pathways, including PI3K, Bruton's tyrosine kinase, and phospholipase Cγ2, which transmit downstream signals that promote B-cell survival and proliferation.[3,4] Phosphatidylinositol 3-kinase consists of four isoforms, α, β, δ, and γ; the α and β isoforms are expressed ubiquitously, whereas δ and γ isoform expression is predominantly restricted to hematopoietic cells.[2,5,6] The PI3Kδ prosurvival pathway has been shown to be activated in B-cell lymphoma and is a therapeutic target for the treatment of NHL.[6-8]

Early-generation inhibitors targeting PI3Kδ include idelalisib (PI3Kδ-specific), duvelisib (PI3Kδ/γ dual inhibitor), and copanlisib (pan-PI3K inhibitor). Single-agent ORRs of 42–59%, 39–70%, 40–64%, and 7–19% have been reported with these early PI3K inhibitors in relapsed or refractory FL, MZL, MCL, and DLBCL, respectively.[7-10] Use of PI3K inhibitors in the clinic has been limited due to safety and tolerability concerns. For instance, a proportion of patients receiving early-generation PI3K inhibitors experience irAEs leading to treatment discontinuation.[11] Common irAEs with early-generation PI3K inhibitors include pneumonitis that has been reported in 2–8% of patients, diarrhea (often late-onset) reported in 41–49% (grade ≥3, 5–15%) of patients, and transaminitis reported in 10–47% (grade ≥3, 2–13%) of patients receiving idelalisib, duvelisib, or copanlisib.[9,12,13] Newer PI3K inhibitors designed to improve safety and tolerability, such as parsaclisib and the dual PI3Kδ and casein kinase-1ε inhibitor umbralisib,[14,15] are in clinical development with potential to enhance treatment benefit for patients with NHL.

Parsaclisib is a next-generation PI3Kδ-selective inhibitor that is structurally different from early-generation PI3Kδ inhibitors, and has demonstrated activity in preclinical models of B-cell malignancy.[14] Results of the phase I/II CITADEL-101 study in a US patient population with relapsed or refractory B-cell malignancies indicated a differentiated safety profile from early-generation PI3K inhibitors with reduced hepatotoxicity observed when parsaclisib was given at a dose of 20 mg QD for 9 weeks, followed by 20 mg QW.[16] Parsaclisib has subsequently been investigated in phase II studies in patients with relapsed or refractory DLBCL,[17] FL,[18] MCL,[19,20] and MZL.[21] Here, we describe the results of a multicenter, open-label, phase Ib dose-escalation study of parsaclisib in Japanese patients with previously treated B-cell lymphoma (CITADEL-111).

2 | METHODS

2.1 | Study design

The purpose of this phase Ib study was to evaluate the safety and tolerability, including DLT and MTD, and pharmacokinetics of parsaclisib in Japanese patients with relapsed or refractory B-cell malignancies including DLBCL, FL, MZL, or MCL (CITADEL-111 study; NCT03314922; JapicCTI-184219). Eligible patients were enrolled between August 2018 and August 2020 at five centers in Japan. The study was carried out according to the ethical principles of the Declaration of Helsinki and local regulatory requirements. All patients provided written informed consent prior to participation in any study-specific procedures.

The administration regimen consisted of initial daily doses of parsaclisib for 8 weeks followed by weekly administration of the same dose until disease progression or unacceptable toxicity. Patients were hospitalized for the first 28 days of treatment (DLT period). To be considered evaluable for tolerability and MTD, patients must have received parsaclisib on a minimum of 23 out of 28 days or have experienced a DLT; patients who received fewer than 23 doses were permitted to be replaced to complete the cohort. Up to 18 patients were to be enrolled.

The starting dose of parsaclisib was 10 mg QD, which was half of the targeted starting dose for phase II studies based on the prior phase I/II CITADEL-101 study in a US patient population.[16] Dose escalation followed a 3 + 3 design and if no DLTs were observed in the initial three patients during the first 28 days of treatment, then the 20-mg dose cohort was initiated and at least 12 patients were treated at this dose to confirm safety if the MTD was not exceeded. If a DLT was observed at the initial dose of 10 mg, then deescalation may be considered.

Dose-limiting toxicities were assessed by the investigator according to NCI Common Terminology Criteria for Adverse Events version 4.03 criteria, and included nonhematologic toxicity of grade 3 or above (with the exception of grade 3 or above nausea, vomiting, or diarrhea adequately controlled with medical therapy within 48 hours); any-grade anemia or thrombocytopenia requiring transfusion, grade 3 thrombocytopenia with bleeding; grade 4 anemia, neutropenia, or thrombocytopenia; febrile neutropenia; and general toxicity requiring dose interruption for more than 1 week or any dose reduction during the first 28 days of treatment. Maximum tolerated dose was defined as one dose level below the dose at which one-third or more of patients (two of six patients) in a cohort reported a DLT. If this lower dose level only had three patients treated, then an additional three patients would be enrolled to confirm a DLT rate at one or fewer of six patients to confirm this dose as the MTD.

Patients continued receiving parsaclisib treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

2.2 | Study cohort

Key eligibility criteria of this study were as follows: Japanese (can trace maternal and paternal Japanese ancestry) patients 20 years of age or older with histologically confirmed B-cell NHL (DLBCL, FL, MZL, or MCL); documented disease progression on at least one prior systemic therapy, with no further standard therapy available (as determined by the investigator); an ECOG performance status of no more than 2; adequate hematologic, hepatic, and renal function; life expectancy of more than 3 months; and willingness to undergo lymph node or tissue biopsy (or provide the most recent archival tissue).

Key exclusion criteria included allogeneic HSCT within the past 6 months or autologous HSCT within the past 3 months, active graft-versus-host disease, or prior treatment with a PI3K inhibitor. Patients with a history of central nervous system lymphoma were also excluded.

2.3 | Study end-points and assessments

Primary study end-points were safety and tolerability, and pharmacokinetics of parsaclisib. Severity of AEs were graded by NCI Common Terminology Criteria for Adverse Events version 4.03 criteria. Adverse events of special interest associated with the PI3K class monitored included skin toxicities (rash, exfoliative dermatitis), gastrointestinal toxicities (colitis, diarrhea, intestinal perforation), and infections (eg, pneumonitis, cytomegalovirus, *Pneumocystis jirovecii*, Herpes simplex, varicella zoster). Laboratory events of special interest included treatment-emergent worsening of grade 3 or 4 neutrophil count decreased and transaminase elevations (ALT and AST). Blood samples for pharmacokinetics analysis were collected predose on days 1, 8, and 15, and postdose on days 1 and 15; urine samples were collected on day 15 from 0 hours (after morning dose) to 8 hours postdose (12 hours if a 12-hour sample was collected). A validated liquid chromatography–dual mass spectroscopy assay was used to analyze parsaclisib plasma concentrations (Incyte Corporation) and urine concentrations (Frontage Laboratories).[22] Pharmacokinetics parameters were calculated using Phoenix WinNonlin version 8.2 software (Certara USA).

Secondary end-points included preliminary assessments of efficacy. Investigators assessed response status according to the Lugano criteria.[23] Computed tomography scan, FDG-PET, or combined PET-CT scan were used according to disease subtype and imaging was carried out (using the same technique [CT, FDG-PET, or PET-CT] as at screening) every 8 weeks through week 24, then every 12 weeks through week 96, and thereafter every 24 weeks until progressive disease. Efficacy parameters included ORR, duration of response, and PFS.

Exploratory end-points were pharmacodynamic biomarker analysis and changes in plasma markers at baseline compared with on-treatment to assess potential correlations with treatment response or resistance, and safety. Markers of B-cell activation (B-cell activating factor, B-cell attracting chemokine 1 [CXCL13], and IL10) and changes in other plasma analytes were analyzed. Individual plasma samples (n = 1) for each patient and time point were frozen and shipped for batch analysis at Olink Proteomics to measure the relative levels of proteins by proximity extension assays.

2.4 | Statistical analysis

All treated patients comprised the full analysis set and the safety population, which included all patients enrolled in the study who received at least one dose of parsaclisib. Patient baseline demographics, clinical characteristics, disposition, and all efficacy analyses were carried out using the full analysis set; all safety analyses were carried out using the safety population. All patients who received at least one dose of parsaclisib and provided at least one postdose plasma sample comprised the pharmacokinetic-/pharmacodynamic-evaluable population. Descriptive summaries were prepared for continuous variables (including number of observations, mean, SD, median, minimum, and maximum) and categorical variables (including number and percentage of patients in each category).

Plasma proteomic analyte expression data, reported as relative units, were analyzed by paired *t* test to compare the means of two matched groups (eg, changes in a marker between cycle 1 day 1 and week 4 for individual patients). Differentially expressed analytes were defined as having at least a 1.5-fold change and with raw *p* values of .05 or less.

All statistical analyses were undertaken using SAS® software version 9 or later (SAS Institute).

3 | RESULTS

3.1 | Patients

Seventeen patients were enrolled in this phase Ib study. Three patients were treated in the 10-mg QD + 10-mg QW dose group and 14 patients in the 20-mg QD + 20-mg QW dose group. The median age (range) was 71 (57–79) years, the majority of patients were women (11 [64.7%]), and FL (9 [52.9%]) was the most common NHL subtype, followed by DLBCL (6 [35.3%]) and MZL (2 [11.8%]) (Table 1). The median (range) number of prior therapies was 3 (1–8); prior systemic cancer therapy included rituximab (17 [100%]), cyclophosphamide (14 [82.4%]), prednisolone, and vincristine sulfate (each 13 [76.5%]). No patient had received a prior HSCT.

At the data cut-off of August 14, 2020, 6 patients (35.3%) remained on study treatment and 11 patients (64.7%) had discontinued treatment due to either progressive disease (9 [52.9%]) or AEs (2 [11.8%]). Parsaclisib exposure is summarized in Table 2.

TABLE 1 Baseline demographics and clinical characteristics of 17 Japanese patients with relapsed or refractory B-cell lymphoma treated with parsaclisib (full analysis set)

Characteristic	Parsaclisib dose level[a]		
	10 mg QD + 10 mg QW (n = 3)	20 mg QD + 20 mg QW (n = 14)	Total (N = 17)
Age, y	74.0 (60–79)	70.5 (57–78)	71.0 (57–79)
>65 y	2 (66.7)	8 (57.1)	10 (58.8)
Sex			
Male	1 (33.3)	5 (35.7)	6 (35.3)
Female	2 (66.7)	9 (64.3)	11 (64.7)
Disease type			
FL	1 (33.3)	8 (57.1)	9 (52.9)
DLBCL	1 (33.3)	5 (35.7)	6 (35.3)[b]
MZL	1 (33.3)	1 (7.1)	2 (11.8)[c]
Time since initial diagnosis, y	4.8 (3.0–6.2)	7.5 (0.9–25.1)	6.2 (0.9–25.1)
Current Ann Arbor stage			
I	0 (0.0)	1 (7.1)	1 (5.9)
II	0 (0.0)	1 (7.1)	1 (5.9)
III	0 (0.0)	7 (50.0)	7 (41.2)
IV	3 (100.0)	5 (35.7)	8 (47.1)
ECOG performance status			
0	3 (100.0)	9 (64.3)	12 (70.6)
1	0 (0.0)	4 (28.6)	4 (23.5)
2	0 (0.0)	1 (7.1)	1 (5.9)
Prior systemic therapies			
1	1 (33.3)	3 (21.4)	4 (23.5)
2	0 (0.0)	3 (21.4)	3 (17.6)
≥3	2 (66.7)	8 (57.1)	10 (58.8)
Prior surgery	2 (66.7)	2 (14.3)	4 (23.5)
Prior radiation therapy	0 (0.0)	5 (35.7)	5 (29.4)
Prior HSCT	0 (0.0)	0 (0.0)	0 (0.0)

Note: Data are shown as n (%) or median (range).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; MZL, marginal zone lymphoma; n, number; QD, once daily; QW, once weekly; wk, weeks; y, years.

[a]Parsaclisib dose level for 8 wk plus parsaclisib dose level after 8 wk.

[b]DLBCL subtypes germinal center (1 patient), nongerminal center (2 patients), unknown (3 patients).

[c]MZL subtypes extranodal (1 patient), splenic (1 patient).

The median duration of treatment was 8.3 (range, 0.3–24.5) months; 10 patients (58.8%) required a dose interruption during the treatment period and 5 patients (29.4%) required a dose reduction. No DLTs occurred during the 28-day DLT observation period in the 6 patients who were enrolled during the dose-escalation phase and dosed at either the 10-mg ($n = 3$) or 20-mg ($n = 3$) dose level. Consequently, the 20-mg dose was selected for dose expansion. A DLT of grade 3 febrile neutropenia on day 28 and grade 4 neutropenia on day 14 (each in 1 patient) occurred at the 20-mg dose level during dose expansion. Parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW was not considered to have exceeded the MTD in Japanese patients.

3.2 | Pharmacokinetics and pharmacodynamics

At cycle 1 day 15, following 10-mg and 20-mg oral administration in the fasted state, the mean ± SD maximum plasma drug concentration of parsaclisib was 1440 ± 502 nM and 2630 ± 530 nM, achieved at a median time to maximum plasma drug concentration of 0.97 and 0.55 hours, respectively, with subsequent biexponential decay. The overall parsaclisib steady-state geometric mean $t_{½}$ was 9.9 hours and dose-independent, with a systemic accumulation ratio of approximately 1.3 with daily dose (Table 3). The apparent oral dose clearance at steady state and volume of distribution were 2.2 ± 0.7 L/h and 31.2 ± 9.8 L, respectively. Mean ± SD

TABLE 2 Summary of parsaclisib exposure in 17 Japanese patients with relapsed or refractory B-cell lymphoma (safety population)

Variable	Parsaclisib dose level[a]		
	10 mg QD + 10 mg QW (n = 3)	20 mg QD + 20 mg QW (n = 14)	Total (N = 17)
Overall treatment,[b] n	3	14	17
Median (range) duration of treatment, d	246.0 (35–744)	309.0 (9–585)	253.0 (9–744)
Patients with dose interruption, n (%)	2 (66.7)	8 (57.1)	10 (58.8)
Patients with dose reduction, n (%)	1 (33.3)	4 (28.6)	5 (29.4)
QD dosing period,[c] n	3	14	17
Median (range) duration of treatment, d	56.0 (35–56)	56.0 (9–57)	56.0 (9–57)
QW dosing period,[d] n	2	10	12
Median (range) duration of treatment, wk	63.5 (28–99)	64.0 (1–76)	64.0 (1–99)

Abbreviations: d, days; n, number; QD, once daily; QW, once weekly; wk, weeks.

[a]Parsaclisib dose level for 8 wk plus parsaclisib dose level after 8 wk.

[b]Duration of treatment (d) = date of last dose − date of first dose + 1.

[c]Duration of treatment during initial QD period = date of last QD dose in the initial QD period − date of first dose + 1.

[d]Duration of treatment during QW period (wk) = ceiling of [(date of last dose − date of first dose in QW period + 1)/7].

minimum plasma drug concentrations following 10 mg or 20 mg QD administration were 227 ± 83.2 nM and 303 ± 155 nM, respectively, which exceed the calculated in vitro IC_{90} (40 nM) for phospho-AKT inhibition, a measure of PI3K pathway pharmacodynamic activity.

Body weight–normalized apparent oral dose clearance at steady state and volume of distribution were comparable between Japanese patients in this study and US patients in the phase I/II CITADEL-101 study,[16] although mean parsaclisib exposures were 65–80% higher in Japanese patients relative to US patients in the phase I/II CITADEL-101 study (Figure S1). Mean (range) percentage of unchanged parsaclisib recovered in urine during the 0- to 8-hour collection interval was 12.1 (5.4–20.4) and renal clearance (mean ± SD) was 0.4 ± 0.2 L/h (Table S1).

To assess the pharmacodynamic activity of parsaclisib, plasma samples collected from 15 patients were analyzed for changes in proteins associated with PI3Kδ inhibition. Analysis of approximately 1000 proteins in samples from patients with FL and MZL (n = 11) identified a set of 23 plasma proteins that were significantly changed following 4 weeks or 8 weeks of QD parsaclisib dosing (Table S2). Among the set were multiple proteins previously reported as biomarkers of PI3Kδ inhibitors that are involved in lymphocyte activation and immune response,[24,25] including CXCL13, CCL17, IL10, MMP9, TNFB, and TNFRSF9 (Figure S2). Following week 8 and the transition to 10 mg or 20 mg QW parsaclisib dosing regimens, parsaclisib-responsive proteins consistently reverted partially or completely to baseline expression levels. This rebound in expression, observed at weeks 12 and 24, is consistent with the lower dose intensity of the QW regimen.

A notable outlier in the proteomic analysis for patients with FL or MZL were samples from one patient with FL who showed minimal change in multiple parsaclisib-responsive proteins (Figure S2A–D). The patient had an early partial response to parsaclisib but showed disease progression within 2 months. The reason for the lack of pharmacodynamic response and rapid disease progression are not currently understood.

Although patients with FL and MZL generally showed comparable trends in response to treatment among pharmacodynamic plasma biomarkers, changes in plasma proteins for patients with DLBCL were less consistent. Among 4 patients with DLBCL, 1 patient who had a partial response showed comparable changes in the set of 23 proteins that were identified in patients with FL and MZL (Figure S2). Among the 3 remaining patients with DLBCL (1 with stable disease and 2 with progressive disease), a majority of the parsaclisib-responsive proteins had smaller or insignificant changes (eg, CXCL13, IL10, CCL17, TNFB, and Fc receptor-like protein 2) whereas a subset of proteins showed significant fold-changes that were equivalent to FL and MZL patients (eg, MMP9, X-C chemokine ligand 1, and CD160).

3.3 | Safety

As of the data cut-off date, all patients experienced at least one TEAE, and 16 patients (94.1%) experienced a TEAE considered by the investigator to be related to parsaclisib treatment. The most common nonhematologic TEAEs were constipation (6 [35.3%]), nausea, and pyrexia (each 4 [23.5%]) (Table 4). Treatment-emergent AEs led to dose interruption in 11 patients (64.7%; 7 patients during QD dosing, 4 patients during QW dosing) and to dose reduction in 5 patients (29.4%; 2 patients during QD dosing, 3 patients during QW dosing). Treatment-emergent AEs of grade 3 or higher occurred in 11 patients (64.7%). Nonhematologic grade 3 or higher TEAEs occurring in 1 patient each were bile duct stenosis (secondary to pancreatitis), hypoalbuminemia, and lymphoma progression (metastases to meninges [lymphomatous meningitis]). All grade 3 or higher TEAEs, except bile duct stenosis and metastases to meninges, occurred during the QD period. Serious TEAEs occurred in 5 patients (29.4%),

TABLE 3 Parsaclisib pharmacokinetic parameter summary with monotherapy on cycle 1 day 15 in 14 Japanese patients with relapsed or refractory B-cell lymphoma (pharmacokinetic-/pharmacodynamic-evaluable population)

Dose	n	C_{max} (nM)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-τ}$ (nM·h)	C_{min} (nM)	CL_{ss}/F (L/h)	V_z/F (L)	Accumulation ratio
10 mg QD	3	1440 ± 502 (1390, 34.9)	1.0 (0.5–2.0)	12.6 ± 4.6 (12.0, 36.6)	12,500 ± 3710 (12,100, 29.6)	227 ± 83.2 (215, 36.6)	1.8 ± 0.6 (1.75, 30.9)	31.3 ± 9.8 (30.3, 31.3)	1.4 ± 0.2 (1.4, 17.1)
20 mg QD	11	2630 ± 530 (2580, 20.2)	0.55 (0.4–1.8)	9.8 ± 2.8 (9.45, 28.9)	20,500 ± 6340 (19,600, 30.9)	303 ± 155 (271, 51.0)	2.3 ± 0.75 (2.2, 32.9)	31.1 ± 10.2 (29.7, 32.9)	1.2 ± 0.1 (1.2, 11.3)
Total	14	-	-	10.4 ± 3.3 (9.9, 30.0)	-	-	2.2 ± 0.7 (2.1, 32.8)	31.2 ± 9.8 (29.8, 31.7)	1.3 ± 0.2 (1.25, 13.1)

Note: Values are mean ± SD (geometric mean, coefficient of variation [CV]%), with exception of time to maximum plasma drug concentration (T_{max}), reported as median (range).

Abbreviations: $AUC_{0-τ}$, area under the concentration-time curve over the dosing interval; CL_{ss}/F, oral dose clearance at steady state; C_{max}, maximum plasma drug concentration; C_{min}, minimum plasma drug concentration; QD, once daily; V_z/F, apparent oral dose volume of distribution.

with pyrexia being the most frequent, experienced by 2 patients (11.8%). Other serious TEAEs experienced by 1 patient each were diarrhea, enteritis infection, febrile neutropenia, metastases to meninges, and pancreatitis.

Adverse events of special interest were reported in 7 patients (41.2%). Three patients experienced TEAEs of diarrhea (1 patient with grade 1 and 2 patients with grade 2) with the time to first onset of 70, 108, and 305 days, and the longest time to resolution of 14, 18, and 67 days; none of the TEAEs of diarrhea led to parsaclisib discontinuation. Rash occurred in 3 patients (2 patients with grade 1 and 1 patient with grade 2), with time to onset of first occurrence of 11, 50, and 312 days, and the longest time to resolution of 5, 8, and 23 days. One patient experienced grade 1 exfoliative dermatitis with onset at day 64 and resolution in 36 days. Two patients experienced grade 3 febrile neutropenia (time to onset 28 and 63 days, time to resolution 10 and 2 days). Varicella zoster infection occurred in 1 patient on day 33 of treatment and resolved in 21 days, was of grade 2 in severity, and led to parsaclisib discontinuation.

Treatment-emergent grade shifts in hematologic laboratory parameters were commonly observed, but most of the postbaseline worsening of hematologic parameters were to a maximum severity of grade 1 or 2 (Table 5). Five patients (29.4%) experienced treatment-emergent new or worsening decreased neutrophils to grade 3 or 4. All events of grade 3 or 4 decreased neutrophil count occurred during the first 8 weeks of treatment with parsaclisib. Most treatment-emergent grade changes in clinical chemistry laboratory parameters were shifts to a maximum severity of grade 1 or 2. Among 16 patients who each had grade 0 ALT or AST values at baseline, all shifts to increased ALT were to grade 1 (5 patients) or grade 2 (2 patients), and all shifts to increased AST were to grade 1 (7 patients). There were no treatment-emergent elevations of ALT or AST to grade 3 or 4.

The most common TEAE that led to parsaclisib dose interruption was decreased neutrophil count (5 [29.4%]); an additional 2 (11.8%) patients had neutropenia that led to dose interruption. Treatment-emergent AEs leading to parsaclisib dose reduction included febrile neutropenia (1 patient), drug eruption and neutropenia in a single patient during the QD period, pancreatitis and pancreatitis relapsing in a single patient, and diarrhea (1 patient) and exfoliative dermatitis (1 patient) during the QW period. Two patients (11.8%) experienced TEAEs that led to treatment discontinuation (1 patient each with varicella zoster infection and pyrexia). There were no TEAEs with a fatal outcome during the study.

3.4 | Efficacy

The ORR was 100% in FL (9 of 9 patients) and MZL (2 of 2 patients), including 22.2% complete responses (2 of 9 patients) in FL; the ORR was 16.7% (1 of 6 patients) in DLBCL (Table 6). The best percentage change of target lesions size from baseline for individual patients is shown in Figure 1; 12 of 16 patients with both baseline and at least one valid postbaseline measurement of target lesions had

TABLE 4 Summary of overall (occurring in ≥2 patients) and grade ≥3 nonhematologic treatment-emergent adverse events (TEAEs), by Medical Dictionary for Regulatory Activities preferred term, in 17 Japanese patients with relapsed or refractory B-cell lymphoma treated with parsaclisib (safety population)

	Any TEAE			Grade ≥3 TEAE		
Preferred term, n (%)	QD dosing period[a] (n = 17)	QW dosing period[b] (n = 12)	Total[c] (N = 17)	QD dosing period[a] (n = 17)	QW dosing period[b] (n = 12)	Total (N = 17)
Constipation	4 (23.5)	2 (16.7)	6 (35.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (11.8)	3 (25.0)	4 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	3 (17.6)	1 (8.3)	4 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	0 (0.0)	3 (25.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Drug eruption	3 (17.6)	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	2 (11.8)	1 (8.3)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	3 (25.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	3 (25.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	1 (5.9)	2 (16.7)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	1 (5.9)	1 (8.3)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dry eye	0 (0.0)	2 (16.7)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dry skin	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Fall	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	0 (0.0)	2 (16.7)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoalbuminemia	2 (11.8)	0 (0.0)	2 (11.8)	1 (5.9)	0 (0.0)	1 (5.9)
Myalgia	1 (5.9)	1 (8.3)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	2 (11.8)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: QD, once daily; QW, once weekly; wk, weeks.

[a]Patients received parsaclisib 10 or 20 mg QD for 8 wk as the initial dose.

[b]Patients received parsaclisib 10 or 20 mg QW following QD dosing.

[c]Patients with a given TEAE in both the QD and QW period are counted only once in the total.

reductions from baseline in sum of product of target lesion diameters. The observed response duration was 1 day to 15.7 months in the nine responders with FL (observed PFS, 1.9–17.5 months), 14.8 and 16.8 months in the two responders with MZL (observed PFS, 16.7 and 22.0 months, respectively), and 12.2 months in the one responder with DLBCL (observed PFS, 13.8 months).

4 | DISCUSSION

Parsaclisib is a next-generation PI3Kδ inhibitor that has been investigated in phase I and II clinical studies in patients with relapsed or refractory DLBCL, FL, MZL, and MCL.[17-21] This phase Ib study investigated the safety and efficacy of parsaclisib in Japanese patients with relapsed or refractory B-cell lymphoma.

No DLTs were observed at the 10 mg parsaclisib dose level, and although two DLTs occurred in one patient each at 20 mg in the dose-expansion phase on the QD schedule, the criteria for MTD was not exceeded at the 20 mg parsaclisib dose level in the Japanese population. The AESIs known to be associated with early-generation PI3K inhibitors, including irAEs (diarrhea/colitis, transaminitis, rash, and pneumonitis) and infections[8,11] were monitored in the CITADEL-111 study. The AESIs reported with parsaclisib included diarrhea, rash, febrile neutropenia, exfoliative dermatitis, and varicella zoster virus. These AESI events with parsaclisib were generally of grade 1 or 2 in severity, apart from grade 3 febrile neutropenia in two patients. One patient experienced a serious TEAE of pancreatitis (grade 2, study days 78 and 145) that resulted in parsaclisib dose interruption on both occurrences; the pancreatitis responded to corticosteroid treatment.

In hematologic and clinical chemistry laboratory assessments, new or worsening decreases in neutrophil count to grade 3 or 4 were observed in 29.4% of Japanese patients treated with parsaclisib (all during the first 8 weeks of treatment); in previous studies in patients with FL or MZL treated with parsaclisib, reported incidences of decreases in neutrophil count to grade 3 or 4 were 13–14%.[18,21] Although elevation in ALT and AST each occurred in 41.2% of patients in our study, the shifts from baseline were to grade 1 or

TABLE 5 Postbaseline worsening of hematology and clinical chemistry laboratory parameters occurring in ≥25% of patients with relapsed or refractory B-cell lymphoma treated with parsaclisib (safety population)

	Total safety population (N = 17)		
	Any postbaseline abnormality	Worst grade postbaseline	
		Grade 3	Grade 4
Hematologic parameters, n (%)			
Neutrophils (decreased)	12 (70.6)	4 (23.5)	1 (5.9)
Leukocytes (decreased)	9 (52.9)	0 (0.0)	0 (0.0)
Platelets (decreased)	7 (41.2)	0 (0.0)	0 (0.0)
Clinical chemistry parameters, n (%)			
Creatinine[a] (increased)	17 (100.0)	0 (0.0)	0 (0.0)
Albumin (decreased)	9 (52.9)	0 (0.0)	0 (0.0)
Calcium (decreased)	8 (47.1)	0 (0.0)	0 (0.0)
Alanine aminotransferase (increased)	7 (41.2)	0 (0.0)	0 (0.0)
Alkaline phosphatase (increased)	7 (41.2)	0 (0.0)	0 (0.0)
Aspartate aminotransferase (increased)	7 (41.2)	0 (0.0)	0 (0.0)
Potassium (increased)	5 (29.4)	0 (0.0)	0 (0.0)
Sodium (decreased)	5 (29.4)	0 (0.0)	0 (0.0)

Note: Parameters graded according to the Common Terminology Criteria for Adverse Events version 4.03 (CTC).

If baseline grade was missing, any postbaseline abnormality (grade 1–4) was considered worsening from baseline.

[a]CTC grade based on changes relative to the upper limit of normal and baseline values.

2; there were no treatment-emergent elevations of ALT or AST to grade 3 or 4. Transaminase elevation was similar in previous studies in patients with NHL treated with parsaclisib, where reported incidences of ALT and AST elevation were 13–26% and 17–23%, respectively.[17,18,21]

Commonly reported nonhematologic TEAEs in Japanese patients treated with parsaclisib were constipation (35.3%), nausea, and pyrexia (23.5% each). In contrast to constipation, diarrhea was the most common TEAE (20–44%) in prior studies in primarily Western populations.[17,18,21] Although diarrhea reported with PI3Kδ inhibitors is believed to be attributable to an on-target autoimmune toxicity,[7,8,11] the reasons for constipation being observed in Japanese patients treated with parsaclisib is not known. Other commonly reported TEAEs with parsaclisib in primarily Western populations were nausea (14–26%), cough (17–22%), rash (14–22%), and pyrexia (13–17%).[17,18,21] Thus, except for a higher frequency of constipation, the safety profile of parsaclisib in Japanese patients appears to be consistent with Western populations.

TABLE 6 Summary of objective response rate (ORR) and best overall response (BOR) in 17 Japanese patients with relapsed or refractory B-cell lymphoma treated with parsaclisib (full analysis set)

NHL subtype	FL (n = 9)	DLBCL (n = 6)	MZL (n = 2)
Objective response,[a] n (%)	9 (100.0)	1 (16.7)	2 (100.0)
95% CI for ORR	66.4–100	0.4–64.1	15.8–100
BOR, n (%)			
CMR/CR	2 (22.2)	0 (0.0)	0 (0.0)
PMR/PR	7 (77.8)	1 (16.7)	2 (100)
NMR/SD	0 (0.0)	1 (16.7)	0 (0.0)
PMD/PD	0 (0.0)	3 (50.0)	0 (0.0)
Not assessed[b]	0 (0.0)	1 (16.7)	0 (0.0)

Abbreviations: CI, confidence interval; CMR/CR, complete metabolic response/complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NMR/SD, no metabolic response/stable disease; PMD/PD, progressive metabolic disease/progressive disease; PMR/PR, partial metabolic response/partial response.

[a]Patients who have best response of CMR/CR or PMR/PR.

[b]No postbaseline response data available.

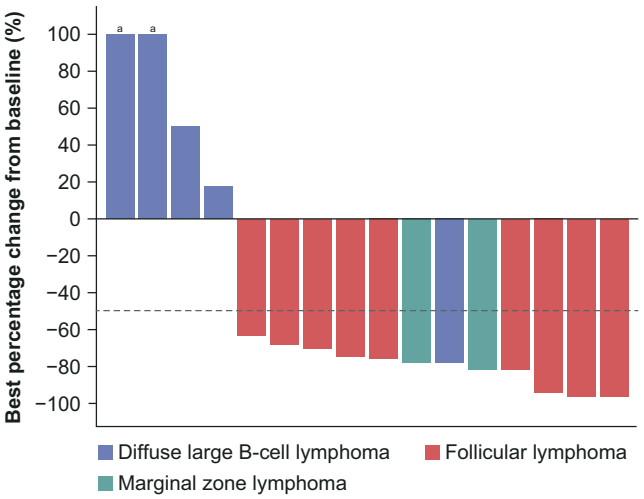

FIGURE 1 Best percentage change from baseline in sum of product of diameters of target lesions following treatment with parsaclisib in 16 Japanese patients with non-Hodgkin lymphoma (full analysis set). [a]Best percentage change from baseline >100%. Data not shown for one patient with diffuse large B-cell lymphoma (no postbaseline response assessment)

Pharmacokinetic analyses indicated that overall parsaclisib exposures were 65–80% higher in Japanese patients relative to Western patients, most likely due to a lower body weight/body mass index in the Japanese population than Western populations. Patients enrolled in the current trial had a median body mass index of 22.1 compared with 27.3 in the phase I/II CITADEL-101 study in a US patient population with B-cell malignancies,[16] and the exposure was not significantly different when pharmacokinetics data were normalized for body weight.

Proteomic analysis of plasma samples confirmed pharmacodynamic response in a set of proteins enriched for factors involved in lymphocyte activation and immune response, including previously described pharmacodynamic biomarkers of PI3Kδ inhibition.[24,25] The majority of parsaclisib-responsive proteins were decreased in Japanese patients receiving treatment, with mean expression levels that were essentially unchanged between week 4 and week 8. A majority of the same parsaclisib-responsive proteins were also identified in the earlier phase I/II CITADEL-101 study[16] of parsaclisib in patients with NHL (unpublished data, 2019, Incyte Corporation). Following transition to the lower dose intensity weekly regimen, parsaclisib-responsive proteins consistently reverted partially or completely to baseline expression levels, reflecting the intermittent relief of target inhibition. Notably, within the set of proteins responsive to parsaclisib treatment, some showed greater or more significant decreases in patients with FL or MZL with an objective response (CXCL13, IL10, TNFB, and CCL17), whereas others changed irrespective of clinical response (TNFRSF9 and MMP9), reflecting the combined effects of PI3Kδ inhibition on both healthy blood cells and lymphoma cells.

Objective responses were observed in patients across all three disease subtypes, with a 100% ORR in FL (9 of 9 patients) and MZL (2 of 2 patients). Two of 9 patients with FL had complete responses (22.2%) and the remaining 7 patients with FL had partial responses. Both patients with MZL and 1 of 6 patients (16.7%) with DLBCL achieved partial responses with parsaclisib treatment. The response in FL and MZL is similar to results of primary analyses reported from the phase II studies with parsaclisib in patients with FL and MZL.[18,21]

In conclusion, parsaclisib exposure in Japanese patients was comparable to that observed in Western patients after normalization for weight and, therefore, no dose adjustments are needed for Japanese patients. Overall, the AE profile was manageable and no new or unexpected AEs were observed in Japanese patients. No clinically significant transaminase elevations occurred. Parsaclisib demonstrated clinical activity, including two complete responses in patients with FL, and responses were durable. The results of this study of parsaclisib in Japanese patients with relapsed or refractory FL or MZL support further clinical development.

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DISCLOSURE

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DATA AVAILABILITY 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 anonymized datasets owned by Incyte for the purpose of conducting legitimate scientific research. Researchers may request anonymized datasets from any interventional study (except phase I 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, Europe, Japan). Data will be available for request after the primary publication or 2 years after the study has ended. Information on Incyte'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-trial-data-sharing.pdf?ver=2020-05-21-132838-960.

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REFERENCES

1. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. *Lancet*. 2017;390:298-310.
2. Allen JC, Talab F, Slupsky JR. Targeting B-cell receptor signaling in leukemia and lymphoma: how and why? *Int J Hematol Oncol*. 2016;5:37-53.
3. Valla K, Flowers CR, Koff JL. Targeting the B cell receptor pathway in non-Hodgkin lymphoma. *Expert Opin Investig Drugs*. 2018;27:513-522.
4. Efremov DG, Turkalj S, Laurenti L. Mechanisms of B cell receptor activation and responses to B cell receptor inhibitors in B cell malignancies. *Cancers*. 2020;12:1393.
5. Jerkeman M, Hallek M, Dreyling M, et al. Targeting of B-cell receptor signalling in B-cell malignancies. *J Intern Med*. 2017;282:415-428.
6. Kienle DL, Stilgenbauer S. Approved and emerging PI3K inhibitors for the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma. *Expert Opin Pharmacother*. 2020;21:917-929.
7. Phillips TJ, Michot JM, Ribrag V. Can next-generation PI3K inhibitors unlock the full potential of the class in patients with B-cell lymphoma? *Clin Lymphoma Myeloma Leuk*. 2021;21:8-20.e23.
8. Sapon-Cousineau V, Sapon-Cousineau S, Assouline S. PI3K inhibitors and their role as novel agents for targeted therapy in lymphoma. *Curr Treat Options Oncol*. 2020;21:51.
9. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28:2169-2178.
10. Lenz G, Hawkes E, Verhoef G, et al. Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with

molecularly defined relapsed or refractory diffuse large B-cell lymphoma. *Leukemia*. 2020;34:2184-2197.
11. Brown JR. Phosphatidylinositol 3 kinase δ inhibitors: present and future. *Cancer J*. 2019;25:394-400.
12. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008-1018.
13. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol*. 2019;37:912-922.
14. Shin N, Stubbs M, Koblish H, et al. Parsaclisib is a next-generation phosphoinositide 3-kinase δ inhibitor with reduced hepatotoxicity and potent antitumor and immunomodulatory activities in models of B-cell malignancy. *J Pharmacol Exp Ther*. 2020;374:211-222.
15. Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2021;39:1609-1618.
16. Forero-Torres A, Ramchandren R, Yacoub A, et al. Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies. *Blood*. 2019;133:1742-1752.
17. Coleman M, Belada D, Casasnovas R-O, et al. Phase 2 study of parsaclisib (INCB050465), a highly selective, next-generation PI3Kδ inhibitor, in relapsed or refractory diffuse large B-cell lymphoma (CITADEL-202). *Leuk Lymphoma*. 2021;62:368-376.
18. Lynch RC, Paneesha S, Avigdor A, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory follicular lymphoma (CITADEL-203) [abstract 2935]. *Blood*. 2020;136:36-37.
19. Mehta A, Trněný M, Walewski J, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor (CITADEL-205) [abstract]. *Blood*. 2020;136:22-23.
20. Zinzani PL, Delwail V, Paneesha S, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory mantle cell lymphoma previously treated with ibrutinib (CITADEL-205) [abstract]. *Blood*. 2020;136:43-44.
21. Phillips TJ, Corradini P, Gurion R, et al. Phase 2 study evaluating the efficacy and safety of parsaclisib in patients with relapsed or refractory marginal zone lymphoma (CITADEL-204) [abstract]. *Blood*. 2020;136:27-28.
22. Li J, Rockich K, Yuska B, et al. An open-label study to assess the effect of itraconazole and rifampin on parsaclisib pharmacokinetics when administered orally in healthy participants. *J Clin Pharmacol*. 2020;60:1519-1526.
23. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059-3068.
24. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123:3390-3397.
25. Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ, γ, is clinically active in advanced hematologic malignancies. *Blood*. 2018;131:877-887.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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