Parsaclisib, a PI3Kδ inhibitor, in relapsed and refractory mantle cell lymphoma (CITADEL-205): a phase 2 study

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Summary

Background Parsaclisib is a potent and highly selective PI3Kδ inhibitor that has shown clinical benefit in patients with relapsed/refractory (R/R) B-cell malignancies. In this phase 2 study (CITADEL-205; NCT03235544, EudraCT 2017-003148-19), the efficacy and safety of parsaclisib was evaluated in patients with R/R mantle cell lymphoma (MCL).

Methods Patients ≥18 years old with pathologically confirmed R/R MCL and prior treatment with 1–3 systemic therapies, with (cohort 1) or without (cohort 2) previous Bruton kinase inhibitor (BTKi) treatment, received oral parsaclisib 20 mg once-daily (QD) for 8 weeks, then either parsaclisib 20 mg once-weekly (weekly dosing group [WG]) or parsaclisib 2.5 mg QD (daily dosing group [DG]). The primary endpoint was objective response rate (ORR).

Findings At the primary analysis data cutoff on January 15, 2021, 53 patients in cohort 1 (BTKi-experienced) (WG, n = 12; DG: n = 41) and 108 patients in cohort 2 (BTKi-naive) (WG, n = 31; DG: n = 77) had received parsaclisib monotherapy. The BTKi-experienced cohort was closed after an interim analysis demonstrated limited clinical benefit. In the BTKi-naive cohort, the ORR (95% CI) for DG (dosing selected for further study) was 70.1% (58.6%–80.0%), with a complete response rate (95% CI) of 15.6% (8.3%–25.6%) and a median duration of response (95% CI) of 12.1 (9.0–not evaluable) months. Treatment-emergent adverse events (TEAEs) occurred among 90.7% (98/108) of all treated patients in the BTKi-naive cohort. Grade ≥3 TEAEs occurred among 62.0% (67/108) of patients, including diarrhoea (13.9%, 15/108) and neutropenia (8.3%, 9/108). Parsaclisib interruption, reduction, or discontinuation due to TEAEs occurred among 47.2% (51/108), 8.3% (9/108), and 25.0% (27/108) of patients, respectively. Fatal TEAEs were experienced by six patients and determined to be treatment-related in one patient.

Interpretation Parsaclisib, a potent, highly selective, PI3Kδ inhibitor demonstrated meaningful clinical benefits and a manageable safety profile (25.0% discontinuation rate, low incidences of individually reported grade ≥3 or serious adverse events) in R/R MCL patients with no prior BTKi therapy. Limited clinical benefit was observed with

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parsaclisib monotherapy in patients who had previously received BTKi treatment. Future development of PI3K inhibitors for NHL will require further investigation of dose optimisation to improve safety and long-term survival.

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Keywords: Mantle cell lymphoma; B-cell lymphoma; Non-Hodgkin lymphoma; PI3K inhibitor; Parsaclisib

Research in context

Evidence before this study

We searched the PubMed database for articles on the use of PI3K inhibitors for the treatment of mantle cell lymphoma (MCL) and identified 160 publications, of which 12 reported clinical trials in MCL. Based on published reports, PI3K inhibitors appear to be associated with class-specific toxicities such as hepatotoxicity (elevations in aminotransferases), pneumonitis, rash, diarrhoea events that can progress to colitis, and opportunistic infections. Parsaclisib, a highly selective PI3Kδ inhibitor, was structurally designed to enhance specificity and limit toxicity, and has demonstrated differentiated tolerability and encouraging clinical outcomes in R/R B-cell lymphoma, including MCL.

Added value of this study

CITADEL-205 is a multicentre, open-label, phase 2 study that evaluated the efficacy and safety of parsaclisib in patients with R/R MCL with or without prior BTK inhibitor treatment; ORR in BTK-naive patients receiving parsaclisib daily dosing was 70%, which compares favourably with ORRs ranging from 33% to 67% with other PI3K inhibitors. Common adverse events included diarrhoea, pyrexia, constipation, and rash, mostly low grade and improved with dose interruptions or reductions.

Implications of all the available evidence

Data from our study suggest that although parsaclisib demonstrated limited clinical benefit in patients who had previously received BTK inhibitor treatment, patients without prior BTK therapy achieve rapid and durable responses indicating that parsaclisib may provide an effective treatment option for this patient population. However, several PI3K inhibitors have had their US Food and Drug Administration indications or marketing authorisation withdrawn owing to feasibility of confirmatory studies, or concerns over increased toxicity and reduced overall survival in patients with indolent NHL or chronic lymphocytic lymphoma. Therefore, further investigations would be required to address safety concerns and identify patients with R/R MCL for whom PI3K inhibitors, such as parsaclisib, could be an alternative treatment to existing therapies.

Introduction

Mantle cell lymphoma (MCL) represents 2%–4% of all B-cell non-Hodgkin lymphoma (NHL) cases in Western countries, and is aggressive and incurable.[1] First-line treatment regimens consist of rituximab plus chemotherapy backbone, with additional agents dependent on patient-specific factors and comorbidities.[2,3] Overall survival (OS) of 3–6 years has been reported following first-line chemotherapy[4]; however, most patients ultimately relapse.[5] Second- and subsequent-lines of therapy include Bruton tyrosine kinase (BTK) inhibitors, non–cross-resistant chemotherapy, and chimeric antigen receptor (CAR) T-cell therapy.[2,3,6] BTK inhibitors (BTKi) approved as second-line therapy for R/R MCL include single-agent ibrutinib,[7,8] acalabrutinib,[9] and zanubrutinib,[10] and pirtobrutinib has recently been approved as a third-line therapy following at least two lines of systemic therapy including a BTKi.[11] Other approved therapies for R/R MCL include lenalidomide,[12,13] bortezomib,[14] and temsirolimus.[15] Given the likelihood of relapse and limited options for later lines of therapy, there is an unmet need for therapies for R/R MCL.

The upregulation of phosphoinositide 3-kinase (PI3K) is a critical driver of growth and survival of B lymphocytes[16,17] and the dysregulation of this pathway, particularly overactivity of the PI3Kδ isoform, plays a key role in the development of B-cell malignancies.[17,18] PI3K inhibitors have demonstrated clinically meaningful efficacy as monotherapy for the treatment of R/R NHLs, with ORRs of 33%–67% in MCL.[16,19,20] However, safety and tolerability limitations continue to challenge the optimisation of this drug class.[17] Several adverse events (AEs) appear to be a class effect (eg, transaminitis, diarrhoea, colitis, pneumonitis, neutropenia, and rash)[21–23] and other AEs, such as hyperglycaemia and hypertension, have been observed with a PI3K inhibitor (copanlisib) that also targets the α-isoform.[21]

Parsaclisib is at least 10,000-fold more selective for PI3Kδ (half maximal inhibitory concentration, IC_{50} = 1 nM) compared with PI3Kα, PI3Kβ, and PI3Kγ.[24,25] Consistent with this, parsaclisib demonstrated differentiated tolerability and encouraging clinical outcomes in the phase 1/2 CITADEL-101 study of patients with R/R NHL, including MCL.[16] Here, we

report the primary results from the open-label, phase 2 CITADEL-205 study, which was conducted to further evaluate the efficacy and safety of parsaclisib among patients with R/R MCL with or without prior BTKi therapy.

Methods

Trial oversight

CITADEL-205 was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. Written informed consent was obtained from each patient before study enrolment.

Study design

CITADEL-205 is a phase 2, multicentre, open-label study that evaluated the efficacy and safety of parsaclisib among patients with R/R MCL (NCT03235544) (Figure S1, Appendix); patients were enrolled in two cohorts: BTKi-experienced (cohort 1) included patients who had previously received treatment with ibrutinib (the only BTKi approved for R/R MCL at study initiation), BTKi-naive (cohort 2) included patients without previous BTKi therapy. The study protocol is available as a Supplemental Appendix. Originally, a sample size of 60 patients per cohort was planned for the entire study. All patients were planned to be allocated in a 1:1 ratio to one of two treatment groups using a randomisation schedule through the interactive web response system: the weekly dosing group (WG) receiving 20 mg of oral parsaclisib once daily (QD) for 8 weeks followed by 20 mg once weekly (QW), or the daily dosing group (DG) receiving 20 mg of oral parsaclisib QD for 8 weeks followed by 2.5 mg QD. The sample size was updated to include an additional 70 patients (BTKi-experienced, 30 patients; BTKi-naive, 40 patients) following a protocol amendment to further understand the safety and efficacy of parsaclisib daily dosing. The BTKi-experienced cohort closed to enrolment with approximately 50 patients enrolled.

After evaluation of emerging safety and efficacy data from this and other parsaclisib monotherapy studies in NHL, the DG was selected for additional study. Subsequently, all patients in both the BTKi-experienced and BTKi-naive cohorts were allocated to this group. Patients in the WG were permitted to switch to daily dosing or 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* (PJP) prophylaxis regimen while receiving parsaclisib and for 2–6 months after their last dose.

Patients

Patients enrolled were at least 18 years or older with pathologically confirmed R/R MCL and overexpression of cyclin D1 or t(11; 14). Patients were required to have prior treatment for MCL with one to three systemic therapies and documented failure after achieving at least a partial response (PR) or documented disease progression after the most recent regimen. Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy had to be present, defined as the presence of at least one lesion measuring greater than 1.5 cm in the longest transverse diameter and 1.0 cm or greater in the longest perpendicular diameter by computed tomography (CT) or magnetic resonance imaging (MRI). Patients had to be willing to undergo an incisional or excisional lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue. Patients were required to have an ECOG performance status (ECOG PS) of 0–2, with adequate haematological, hepatic, and renal function.

Patients were excluded if they had a history of central nervous system lymphoma, prior treatment with a PI3Kδ or pan-PI3K inhibitor, had undergone an allogenic stem cell transplant within 6 months or an autologous stem cell transplant within 3 months, or had active graft-versus-host disease. Patients were also excluded if they were taking immunosuppressive therapy or receiving anticancer medications or investigational drugs within protocol-defined intervals prior to the study. Concurrent use of anticancer therapy or potent CYP3A4 inhibitors or inducers was not allowed. A history of stroke, intracranial haemorrhage, or clinically significant cardiac disease within the past 6 months, chronic or current active infectious disease requiring systemic treatment (including human immunodeficiency virus, hepatitis B virus, and hepatitis C virus), or exposure to a live vaccine within 30 days of dosing were also not allowed.

Study endpoints and assessments

The primary study endpoint was ORR, determined by independent review committee (IRC) assessment by CT or MRI using the Lugano classification system.[26] Secondary endpoints included IRC-determined 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), DOR and progression-free survival (PFS) both determined by IRC, OS, and safety and tolerability. Measurable disease and bone marrow examinations were performed at baseline to determine tumour status—if disease was present at baseline, a bone marrow biopsy was required to confirm CR.

Safety assessments included monitoring of the frequency, duration, and severity of AEs (severity measured by CTCAE v4.03; grades 1–5). AEs of special interest were defined as colitis, diarrhoea, exfoliative dermatitis, febrile neutropenia, rash, intestinal perforation, pneumonitis, and pneumonia. Patients were

followed as part of standard safety monitoring for infections including PJP, cytomegalovirus, herpes simplex virus, and varicella zoster virus. Laboratory events of special interest included decreased neutrophil count, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST). Physical examinations, vital signs, 12-lead electrocardiograph (ECG), ECOG PS, and clinical laboratory measurements were performed.

Exploratory endpoints in the study included profiling blood biomarkers at baseline and on-treatment. High-content multiplex proteomic analysis of plasma samples was performed by Olink Proteomics, using a proximity extension assay platform to measure relative protein levels of approximately 1000 analytes. Assessed analytes included proteins involved in lymphocyte activation and immune response, some of which are elevated in NHLs (eg, CXCL13/B-cell attracting chemokine 1). Analyte expression data were analyzed by paired *t* test, and differentially expressed analytes were defined as having at least a 1.5-fold change and with false discovery rate (FDR; expected false positive/[false positive + true positive])-adjusted p-values of 0.05 or less (Table S1, Appendix).

Statistical analyses

Based on available data at the time of the trial design, a sample size of approximately 100 patients in the BTKi-naive cohort was selected so that, if the true ORR was 60% for patients in both treatment groups, there would be an approximate 97% probability of observing the lower bound of the 95% confidence interval (CI) of ORR ≥40%. 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 analyses of efficacy data) and the safety population (used for all safety analysis). The pharmacokinetic/pharmacodynamic evaluable population included patients who received at least one dose of parsaclisib and provided at least one post-dose plasma sample.

This was not a randomised study and no statistical comparisons were planned between treatment groups. Descriptive summaries for continuous and categorical data were reported and 2-sided 95% CI were calculated for each cohort where appropriate. Patients who were initially assigned to the WG who switched to daily dosing 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 IRC.

Role of the funding source

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

Results

Patient demographics and disposition

Between January 17, 2018 and January 29, 2020, 108 patients who were BTKi-naive were enrolled from 50 international study sites into cohort 2 and received parsaclisib, including 31 patients in the WG and 77 patients in the DG (Fig. 1). Ten patients switched from the WG to the DG after starting the 20 mg QW period. In the total population of BTKi-naive patients, the median age was 72.0 years (range, 43–90), 79.6% (86/108) of patients were male, and 81.5% (88/108) of patients were White/Caucasian. At baseline, most patients had an ECOG status of 0 or 1, advanced diseased (Ann Arbor stage IV), and a Mantle Cell Lymphoma International Prognosis Index (MIPI) risk category of intermediate or high. The median number of prior therapies was 1.0 (range, 1–3) and 43.5% (47/108) of patients were refractory to their most recent prior therapy (Table 1).

A total of 53 patients who were BTKi-experienced (12 WG; 41 DG) had been enrolled in cohort 1 before it was closed (30 January 2020) (Fig. 1). An interim analysis determined that the observed ORR in BTKi-experienced patients did not demonstrate a clinically meaningful benefit. Baseline characteristics for BTKi-experienced patients are presented in Table S2 (Appendix) and full results for this cohort are presented in the supplemental material (Appendix).

In the BTKi-naive cohort, as of the January 15, 2021 primary analysis cutoff date, 22 patients in the WG had discontinued treatment and nine remained on treatment, and 56 patients in the DG had discontinued treatment and 21 remained on treatment (Table S3, Appendix). In the DG, the primary reason for treatment discontinuation was progressive disease (39.0% [30/77]) and AEs (29.9% [23/77]). The median duration of parsaclisib treatment in the DG was 7.9 months (range, 1.7–27.4 months) and the median follow-up was 18.2 months (11.6–35.9 months) from the first dose to the data cutoff date. Patient disposition for those enrolled in the BTKi-experienced cohort is summarised in Table S4 (Appendix).

Efficacy

As of the data cutoff date, in the BTKi-naive cohort, IRC-determined ORR for patients in the DG was 70.1% (95% CI 58.6%–80.0%), with a complete response rate (CRR) of 15.6% (95% CI 8.3%–25.6%; Table 2). Stable disease was observed as best overall response among 20.8% (16/77) of patients in the DG. The ORR based on investigator assessment was 81.8% (95% CI 71.4%–89.7%) and the CRR was 27.3% (95% CI 17.7%–38.6%) in the DG. In a subgroup analysis of IRC-determined ORR based

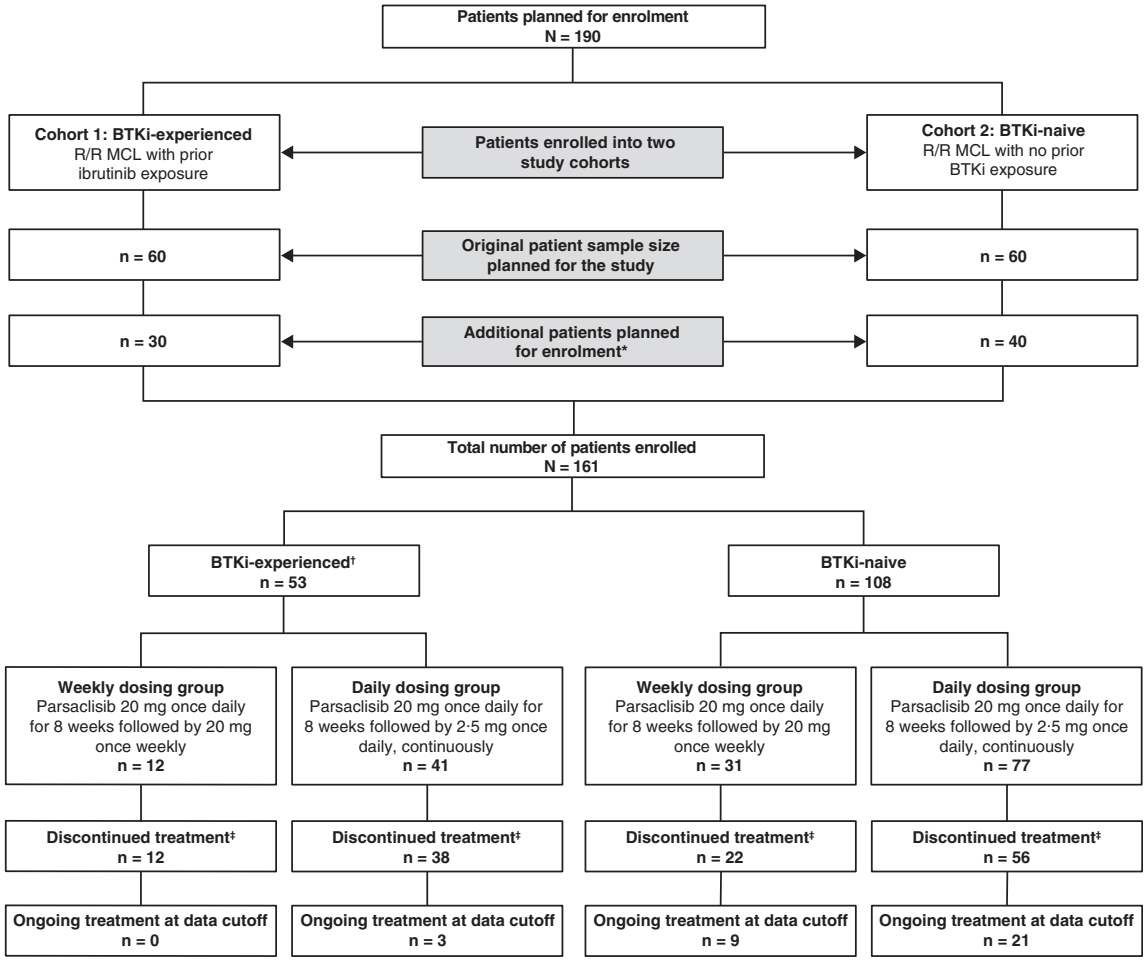

Fig. 1: **CITADEL-205 patient disposition.** BTKi = Bruton tyrosine kinase inhibitor, R/R MCL = relapsed/refractory mantle cell lymphoma. *Following a protocol amendment, the sample size was updated to include an additional 70 patients to further understand the safety and efficacy of the selected dose. †The BTKi-experienced cohort was closed to further enrolment after approximately 50 patients were enrolled. ‡See Tables S3 and S4 (Appendix) for primary reasons for discontinuing treatment in the BTKi-naive and BTKi-experienced cohorts, respectively.

on patient baseline characteristics, response rates in subgroups were generally consistent with the primary analysis in the total population and for the DG (Figure S2, Appendix).

Among all evaluable patients in the DG with baseline and at least one post baseline assessment, 95.7% (66/69) experienced tumour regression, and among those patients 84.8% (56/66) achieved a greater than 50% reduction in target lesion size from baseline (Fig. 2). The median percentage change from baseline in target lesion size as assessed by IRC was –75.1% (range, –100.0% to 73.0%) in the DG.

The median time to response for patients with a CR or PR was 8.1 weeks in the DG; response was observed by the time of the first planned assessment (week 8) among 88.9% (48/54) of responders (Fig. 3). The median DOR was 12.1 months (95% CI 9.0–not evaluable; Fig. 3) in the DG. The median PFS was 13.6 months (95% CI 10.0–16.9; Fig. 3), with estimated 6- and 12-month rates of 69.0% (95% CI 56.5%–78.6%) and 52.1% (95% CI 38.6%–64.0%), respectively. The median OS was not reached in the DG (Fig. 3) and the estimated 6- and 12-month survival rates were 89.4% (95% CI 79.8%–94.5%) and 78.5% (95% CI 67.3%–86.2%), respectively. Data for the WG data are summarised in Figure S3 (Appendix).

Among the 53 patients who had received prior ibrutinib treatment and were enrolled in the BTKi-experienced cohort, the ORR by IRC was 30.2% (95% CI 18.3%–44.3%) with one CR and 15 PRs (Table S5, Appendix). The observed DOR for the 16 responders ranged from 1.9 to 15.8 months and the observed PFS for all 53 patients ranged from 1.9 to 4.1 months. The best percentage change from baseline in target tumour lesion for patients treated in the BTKi-experienced cohort is summarised in Figure S4 (Appendix).

Characteristic	Weekly dosing group[a] (n = 31)	Daily dosing group (n = 77)	All treated patients (N = 108)
Age, median (range), years	74.0 (43–89)	72.0 (51–90)	72.0 (43–90)
≥65 years, n (%)	25 (80.6)	60 (77.9)	85 (78.7)
Male, n (%)	26 (83.9)	60 (77.9)	86 (79.6)
Race, n (%)			
White/Caucasian	24 (77.4)	64 (83.1)	88 (81.5)
Black/African American	0	2 (2.6)	2 (1.9)
Asian	0	1 (1.3)	1 (0.9)
Other	5 (16.1)	3 (3.9)	8 (7.4)
Missing	2 (6.5)	7 (9.1)	9 (8.3)
ECOG performance status, n (%)			
0	16 (51.6)	47 (61.0)	63 (58.3)
1	11 (35.5)	26 (33.8)	37 (34.3)
2	4 (12.9)	4 (5.2)	8 (7.4)
MIPI risk category, n (%)			
Low (0–3)	6 (19.4)	14 (18.2)	20 (18.5)
Intermediate (4–5)	6 (19.4)	21 (27.3)	27 (25.0)
High (6–11)	18 (58.1)	42 (54.5)	60 (55.2)
Missing	1 (3.2)	0	1 (0.9)
Ann Arbor staging, n (%)			
I	1 (3.2)	8 (10.4)	9 (8.3)
II	4 (12.9)	13 (16.9)	17 (15.7)
III	3 (9.7)	8 (10.4)	11 (10.2)
IV	21 (67.7)	48 (62.3)	69 (63.9)
Missing	2 (6.5)	0	2 (1.9)
Time since diagnosis, median (range), years	3.6 (0.1–20.9)	3.5 (0.1–16.9)	3.6 (0.1–20.9)
Number of prior systemic regimens, median (range)	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)
Prior therapies by WHO drug class, n (%)			
Anti-CD20 mAb	30 (96.8)	75 (97.4)	105 (97.2)
Nitrogen mustard analogue	29 (93.5)	74 (96.1)	103 (95.4)
Vinca alkaloids and analogs	21 (67.7)	57 (74.0)	78 (72.2)
Anthracyclines and related substances	21 (67.7)	54 (70.1)	75 (69.4)
Glucocorticoids	20 (64.5)	54 (70.1)	74 (68.5)
Status to most recent prior therapy, n (%)			
Relapsed	16 (51.6)	38 (49.4)	54 (50.0)
Refractory	13 (41.9)	34 (44.2)	47 (43.5)
Unknown	2 (6.5)	5 (6.5)	7 (6.5)

BTKi = Bruton tyrosine kinase inhibitor, ECOG = Eastern Cooperative Oncology Group, mAb = monoclonal antibody, MIPI = Mantle Cell Lymphoma International Prognostic Index, QD = once daily, QW = once weekly, WHO = World Health Organisation. [a]Includes 10 patients who switched 20 mg QW to 2.5 mg QD parsaclisib.

Table 1: **Baseline demographics and clinical characteristics (BTKi-naive cohort).**

Response	Weekly dosing group[a] (n = 31)	Daily dosing group (n = 77)	All treated patients (N = 108)
Best overall response, n (%)			
Complete response	7 (22.6)	12 (15.6)	19 (17.6)
Partial response	13 (41.9)	42 (54.5)	55 (50.6)
Stable disease	4 (12.9)	16 (20.8)	20 (18.5)
Progressive disease	1 (3.2)	3 (3.9)	4 (3.7)
Not estimable/assessed	6 (19.4)	4 (5.2)	10 (9.3)
ORR, % (95% CI)	64.5 (45.4–80.8)	70.1 (58.6–80.0)	68.5 (58.9–77.1)
CRR, % (95% CI)	22.6 (9.6–41.1)	15.6 (8.3–25.6)	17.6 (10.9–26.1)

BTKi = Bruton tyrosine kinase inhibitor, CI = confidence interval, CRR = complete response rate, ORR = objective response rate, QD = once daily, QW = once weekly. [a]Includes 10 patients who switched from 20 mg QW to 2.5 mg QD parsaclisib.

Table 2: **Best overall response, and objective response and complete response rate among patients receiving parsaclisib by independent review committee review (BTKi-naive cohort).**

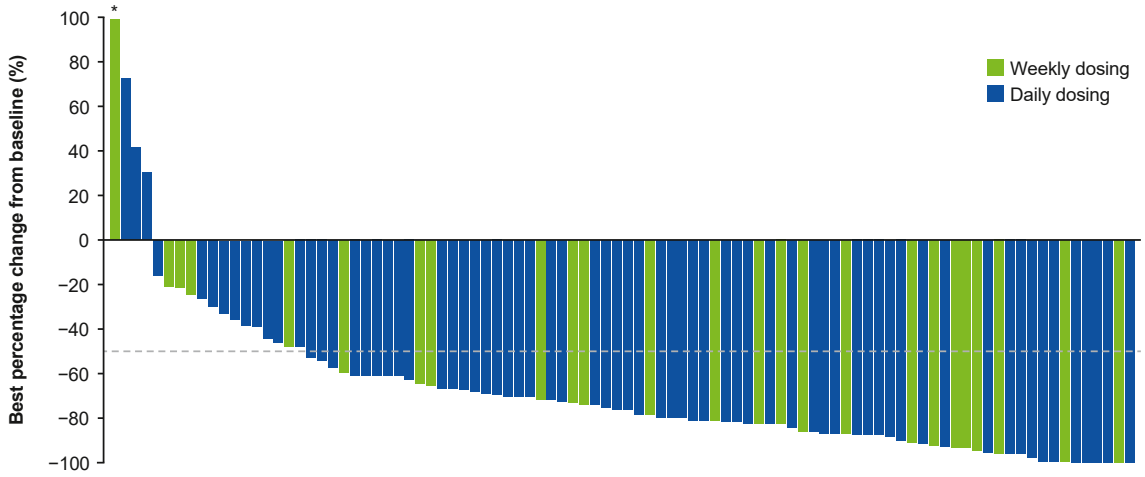

Fig. 2: **Best percentage change from baseline in target lesion size by independent review committee (BTKi-naive cohort).** *Patients had best percentage change >100%. BTKi = Bruton tyrosine kinase inhibitor.

Safety

The safety population in the BTKi-naive cohort included all patients who received at least one dose of parsaclisib (n = 108). TEAEs occurred in 98 (90.7%) patients overall and in 69 (89.6%) patients in the DG (Table 3). The most common TEAEs were diarrhoea (overall, 37/108 [34.3%]; daily dosing, 31/77 [40.3%]), pyrexia (overall, 19/108 [17.6%]; daily dosing, 13/77 [16.9%]),

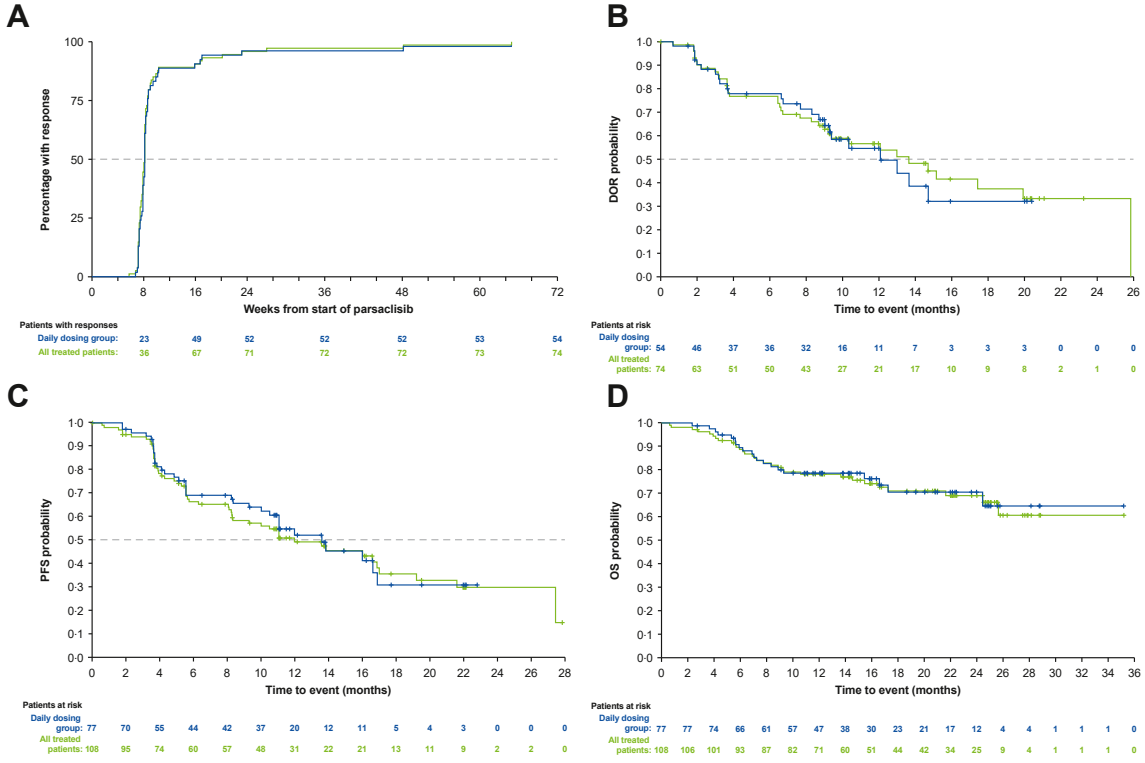

Fig. 3: **Cumulative time to response curves (A), and Kaplan–Meier estimates of duration of response (DOR; B) and progression-free survival (PFS; C) by independent review committee, and overall survival (OS; D) in the daily dosing group (blue) and all treated patients (green) (BTKi-naive cohort).** BTKi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

Preferred term (MedDRA), n (%)	Daily dosing group (n = 77)		All treated patients (N = 108)	
	Any	Grade ≥3	Any	Grade ≥3
Any TEAE	69 (89.6)	49 (63.6)	98 (90.7)	67 (62.0)
Diarrhoea	31 (40.3)	14 (18.2)	37 (34.3)	15 (13.9)
Pyrexia	13 (16.9)	1 (1.3)	19 (17.6)	2 (1.9)
Constipation	11 (14.3)	0	14 (13.0)	1 (0.9)
Asthenia	10 (13.0)	1 (1.3)	12 (11.1)	2 (1.9)
Neutropenia	9 (11.7)	7 (9.1)	12 (11.1)	9 (8.3)
Rash	11 (14.3)	3 (3.9)	12 (11.1)	3 (2.8)
Cough	9 (11.7)	0	11 (10.2)	0
Nausea	7 (9.1)	2 (2.6)	11 (10.2)	2 (1.9)
Back pain	6 (7.8)	1 (1.3)	10 (9.3)	1 (0.9)
Fatigue	8 (10.4)	1 (1.3)	10 (9.3)	1 (0.9)
Hypokalaemia	9 (11.7)	3 (3.9)	10 (9.3)	4 (3.7)
Anaemia	6 (7.8)	2 (2.6)	9 (8.3)	3 (2.8)
Arthralgia	5 (6.5)	0	7 (6.5)	0
Blood creatinine increased	5 (6.5)	0	7 (6.5)	0
Colitis	7 (9.1)	4 (5.2)	7 (6.5)	4 (3.7)
Thrombocytopenia	5 (6.5)	3 (3.9)	7 (6.5)	3 (2.8)
Weight decreased	7 (9.1)	1 (1.3)	7 (6.5)	1 (0.9)
Decreased appetite	6 (7.8)	1 (1.3)	6 (5.6)	1 (0.9)
Hyperuricaemia	3 (3.9)	0	6 (5.6)	2 (1.9)
Oedema peripheral	4 (5.2)	0	6 (5.6)	1 (0.9)

BTKi = Bruton tyrosine kinase inhibitor, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.

Table 3: **Most common any grade and grade ≥3 TEAEs among patients receiving parsaclisib (occurring in ≥5% of patients in the total population at any grade) (BTKi-naive cohort).**

constipation (overall, 14/108 [13.0%]; daily dosing, 11/77 [14.3%]), and rash (overall, 12/108 [11.1%], daily dosing, 11/77 [14.3%]). TEAEs led to parsaclisib discontinuation among 27 patients (25.0%) overall and among 23 patients (29.9%) in the daily dosing group; most frequent TEAEs resulting in parsaclisib discontinuation were diarrhoea (overall, 12/108 [11.1%], daily dosing, 12/77 [15.6%]), colitis (overall, 5/108 [4.6%], daily dosing, 5/77 [6.5%]), and hypokalaemia (overall, 3/108 [2.8%], daily dosing, 2/77 [2.6%]). In the total population of BTKi-naive patients, 51 (47.2%) and nine (8.3%) patients required treatment interruption or dose reductions, respectively, due to TEAEs, and in the DG, 39 (50.6%) and seven (9.1%) patients, respectively. Treatment-related TEAEs were reported in 72 (66.7%) patients overall and in 54 (70.1%) patients in the DG. The most common treatment-related TEAEs were diarrhoea (overall, 27/108 [25.0%]; DG, 24/77 [31.2%]), neutropenia (overall, 10/108 [9.3%]; DG, 8/77 [10.4%]), and rash (overall, 10/108 [9.3%]; DG, 10/77 [13.0%]).

Grade ≥3 TEAEs occurred in 67 patients (62.0%) in the total population and in 49 patients (63.6%) in the DG in the BTKi-naive cohort. Grade ≥3 TEAEs that occurred in at least 5% of patients in the total population were diarrhoea (overall, 15/108 [13.9%]; DG, 14/77 [18.2%]) and neutropenia (overall, 9/108 [8.3%]; DG, 7/77 [9.1%]); 37.0% of patients in the total population had grade ≥3 TEAEs that were considered treatment-related (most commonly diarrhoea, 13/108 [12.0%] and neutropenia, 7/108 [6.5%]). The median time to onset for any grade and grade ≥3 diarrhoea was 2.8 and 4.3 months, respectively. Serious TEAEs occurred in 46 patients (42.6%) in the total population and 35 patients (45.5%) in the DG. Serious TEAEs occurring in at least 2% of patients in the total population were diarrhoea (overall, 10/108 [9.3%]; DG, 10/77 [13.0%]), colitis (overall, 5/108 [4.6%]; DG, 5/77 [6.5%]), hypokalaemia (overall, 3/108 [2.8%]; DG, 2/77 [2.6%]), and pyrexia (overall, 3/108 [2.8%]; DG, 2/77 [2.6%]). There were eight TEAEs with fatal outcome, all of which occurred among five patients in the DG; three fatal TEAEs occurred in the same patient (leukocytosis, acute myelomonocytic leukaemia, and acute kidney injury), and the remaining five TEAEs with fatal outcome occurred among the other four patients (septic shock and staphylococcal endocarditis in one patient; and atrial fibrillation, ECOG PS worsened, and sudden death in one patient each).

Among the AEs of special interest, in addition to diarrhoea and rash (presented above), colitis occurred in seven patients in the total population in the BTKi-naive cohort (6.5%; all in the DG); cytomegalovirus infection in three patients (2.8%; two patients in the DG), pneumonia in two patients (1.9%; all in the DG), pneumonitis and varicella zoster virus in two patients each (1.9%; one patient in the DG), and dermatitis exfoliative,

febrile neutropenia, herpes simplex virus infection, and PJP in one patient each (0.9%; all in the DG except dermatitis exfoliative in WG; Table S6, Appendix). Of note, 89.8% (97/108) of patients in the total population received trimethoprim/sulfamethoxazole as a concomitant medication during the study.

The most common new or worsening haematology laboratory parameters for the total population in the BTKi-naive cohort included decreases in neutrophils (58/108 [53.7%]), platelets (36/108 [33.3%]), and haemoglobin (34/108 [31.5%]) (Table 4). Any grade or grade 3 increases in ALT occurred among 30.6% (33/108) and 4.6% (5/108) of patients, respectively, and increases in AST occurred among 25.9% (28/108) and 2.8% (3/108) of patients, respectively.

A summary of AEs reported in patients enrolled in the BTKi-experienced cohort is presented in Table S7 (Appendix). There were four TEAEs with fatal outcome reported among BTKi-experienced patients; three (neutropenia, pneumonia, and septic shock) were considered related to study treatment in one patient (DG).

Biomarker analysis

Plasma samples for the exploratory biomarker analysis were available for 93 patients from the BTKi-naive cohort. Among patients with a CR or PR, a set of plasma proteins enriched for cytokines, chemokines, and transmembrane receptors that function in lymphocyte activation, migration, and proliferation was differentially detected following 8 weeks of 20 mg QD of parsaclisib (Table S8, Appendix). Effects were maintained almost completely following transition to 2.5 mg QD of parsaclisib, indicating a sustained high level of target inhibition (Figure S5, Appendix).

Discussion

In this study, 77 patients with R/R MCL who were BTKi-naive were treated with parsaclisib 20 mg QD for 8 weeks followed by 2.5 mg QD (DG). The median age was 72.0 years, and 94.8% of patients had an ECOG status of 0 or 1, representative of the R/R MCL patient population. At baseline, most patients had high-risk disease according to MIPI score, Ann Arbor stage IV disease, and half of the patients had relapsed disease. Taken together, these data are consistent with a high-risk population.

Patients in the DG with no prior treatment with a BTKi achieved an ORR of 70.1%, including 15.6% of patients who achieved a CR, and a median DOR of 12.1 months, comparable with other treatments under investigation in this patient population. In phase 2 studies of patients with R/R MCL who received BTKi therapy, reported ORRs and median DORs range from 67% to 84% and 17.5–25.5 months, respectively.[27–29] In addition, these results are consistent with those observed in the phase 1/2 CITADEL-101 trial with single-agent parsaclisib in other B-cell malignancies.[16] Similarly, in the phase 2 studies of patients with follicular lymphoma (FL) (CITADEL-203, NCT03126019) and marginal zone lymphoma (MZL) (CITADEL-204, NCT03144674) treated with the DG regimen, parsaclisib monotherapy resulted in ORRs of 77.7% and 58.3%, and DORs of 14.7 and 12.2 months, respectively.[30,31] Taken together, these data suggest that parsaclisib monotherapy achieves a consistent treatment benefit in patients with NHL, particularly those who have not received prior therapy with a BTKi. In the DG, the median time to response (8.1 weeks) was rapid with 88.9% of responses observed by the first planned assessment (week 8). The median DOR (12.1 months) and median PFS (13.6 months) were both durable. Activity of parsaclisib in MCL was broad and deep; 66 of 69 evaluable patients in the DG demonstrated a reduction in target lesions from baseline, and among them, 56 achieved a >50% reduction in target lesions.

The safety profile of parsaclisib in this study is consistent with that of similar studies of parsaclisib monotherapy in other B-cell lymphomas[16,30,31] and the known profile of other PI3K inhibitors.[21–23] The most commonly reported TEAEs were AEs frequently reported among the PI3K inhibitor drug class, including diarrhoea, pyrexia, constipation, and rash, most of which were low-grade and manageable by dose interruptions or reductions. Grade 3 or higher TEAEs

Preferred term, n (%)	Daily dosing group (n = 77)			All treated patients (N = 108)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Neutrophils decreased	47 (61.0)	5 (6.5)	4 (5.2)	58 (53.7)	6 (5.6)	5 (4.6)
Haemoglobin decreased	25 (32.5)	3 (3.9)	NA	34 (31.5)	3 (2.8)	NA
Platelets decreased	25 (32.5)	3 (3.9)	2 (2.6)	36 (33.3)	5 (4.6)	4 (3.7)
ALT increased	24 (31.2)	2 (2.6)	0	33 (30.6)	5 (4.6)	0
AST increased	19 (24.7)	2 (2.6)	0	28 (25.9)	3 (2.8)	0

NA = CTC grade is not applicable to the parameter,. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BTKi = Bruton tyrosine kinase inhibitor, CTC = Common Terminology Criteria, CTCAE = Common Terminology Criteria for Adverse Events.

Table 4: **New or worsening laboratory abnormalities (worst grade post baseline) occurring in patients receiving parsaclisib (BTKi-naive cohort).**

occurred in 62.0% of all treated patients, similar to what was observed in patients with FL (CITADEL-203) and MZL (CITADEL-204) treated with parsaclisib; the most frequently experienced grade ≥3 TEAE was diarrhoea which had a median time to onset of 4.3 months. Thirty percent of patients in the DG discontinued parsaclisib treatment due to TEAEs, the most common of which were gastrointestinal toxicities and hypokalaemia. It is worth noting that the median duration on study treatment of 7.9 months (range: 1.7–27.4) in BTKi-naive patients in the DG was clinically meaningful, providing sufficient time for a response; at data cutoff, 21 (27.3%) patients in this group were receiving ongoing treatment.

Parsaclisib is highly selective for the PI3Kδ isoform and was structurally designed to reduce PI3Kδ-related hepatotoxicities including elevations in ALT or AST.[24,25] In this study, grade ≥3 increased ALT or AST occurred in 4.6% and 2.8% of BTKi-naive patients overall, respectively, comparing favourably to other PI3K inhibitors.[22,23] No TEAEs of increased ALT or AST resulted in parsaclisib discontinuation. Few ALT and AST elevations have also been observed in studies using copanlisib, a dual inhibitor of PI3Kδ and PI3Kα isoforms. However, copanlisib had clinically relevant high-grade hypertension and hyperglycaemia that appear to be PI3K α-specific toxicities.[21]

Newly approved therapies for patients with R/R NHLs have led to improvements in safety and clinical outcomes. Approved treatments for patients with R/R MCL include BTKis, protease inhibitors, mTOR inhibitors, immunomodulators, and CAR-T cell therapy. Following positive phase 3 trials, the treatment landscape has moved increasingly to the use of BTKis as the preferred second-line treatment for advanced MCL. BTKis including ibrutinib, acalabrutinib, and zanubrutinib are the preferred choice of treatment for patients with MCL who have received at least one prior therapy, with ORRs ranging from 66 to 85%, and median DOR of ≥14.0 months.[27–29,32] The newer-generation BTKis, acalabrutinib and zanubrutinib, are associated with improved safety, including reduced frequency of cardiotoxicity, in patients with indolent NHL and chronic lymphocytic lymphoma (CLL).[33–35] Another BTKi, pirtobrutinib, was recently approved for the treatment of R/R MCL after at least two lines of systemic therapy including a BTKi, based on results from a phase 1/2 clinical trial; patients with MCL who were BTKi-experienced achieved an ORR of 54%.[36,37] While parsaclisib demonstrated significant and durable responses in BTKi-naive patients, it did not demonstrate significant clinical benefit in patients who received prior BTKi therapy.

Recently, PI3K inhibitors including umbralisib, idelalisib, and duvelisib have had approvals withdrawn based on emerging data from confirmatory studies of increased toxicity and reduced OS in patients with indolent NHL or CLL.[38–41] In light of these findings, any future development of PI3K inhibitors for NHL will inevitably require extensive investigation of dose optimisation for safety and demonstrable long-term survival benefits. Although parsaclisib demonstrated meaningful clinical benefits and a manageable safety profile (discontinuation rate of 25.0%, and low incidences of individually reported grade ≥3 or serious adverse events) in BTKi-naive patients with R/R MCL in the current study, further investigations would be required to address the concerns discussed above, and to identify patients with R/R MCL for whom parsaclisib may provide a more favorable treatment alternative to BTKis (for example, patients with R/R MCL who are ineligible for or intolerant of BTKis).

Parsaclisib, a potent and highly selective PI3Kδ inhibitor, demonstrated meaningful, deep, rapid, and durable responses, and a manageable safety profile among patients with R/R MCL who had no prior BTKi treatment. Limited clinical benefits were noted in patients who had previously received BTKi therapy. Considering that the treatment landscape for R/R MCL has moved increasingly to the use of BTKis as the preferred second-line therapy, the role of PI3K inhibitors, including parsaclisib, in the treatment of R/R MCL, would require further investigation.

Contributors

All authors contributed to the acquisition, analysis, and interpretation of data, to the drafting and critical review of the manuscript, and provided approval of the final version to be published. PLZ, AM, FZ, DJD, WJiang, and AG accessed and verified data presented in this 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, 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

PLZ reports consulting or advisory role, and involvement of speakers bureau for Beigene, Bristol Myers Squibb, Celltrion, EUSA Pharma, Gilead, Incyte Corporation, Janssen-Cilag, Kyowa Kirin, Merck Sharp & Dohme, Novartis, Roche, Servier, Takeda, and TG Therapeutics; advisory role for ADC Therapeutics, Sandoz, and Secura Bio. MTrněný reports honoraria, consulting or advisory role, travel and accommodations expenses for AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Roche, and Takeda; honoraria, consulting or advisory role for Amgen, Incyte Corporation, and MorphoSys. VR reports research funding for ArgenX and Astex; membership on a board or advisory committee for Bristol Myers Squibb, Epizyme, Gilead, GlaxoSmithKline, Incyte Corporation, Infinity, Merck Sharp & Dohme, Nanostring, and Roche; membership on a board or advisory committee, honoraria for PharmaMar; membership on a board or advisory committee, consultancy for

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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.2023.102131.

References

1 Chihara D, Nastoupil LJ, Williams JN, Lee P, Koff JL, Flowers CR. New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy. *Expert Rev Anticancer Ther*. 2015;15:531–544.
2 Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv62–iv71.
3 National Comprehensive Cancer Network. *B-cell lymphomas*; 2021. Version 4.2021.
4 Vose JM. Mantle cell lymphoma: 2017 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol*. 2017;92:806–813.
5 Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J*. 2019;9:50.
6 Kite Pharma Inc. *TERCARTUS (brexucabtagene autoleucel) prescribing information*; 2021. https://www.fda.gov/media/140409/download. Accessed August 31, 2022.
7 Janssen-Cilag International NV. *IMBRUVICA (ibrutinib) EPAR*; 2022. https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf. Accessed August 31, 2022.
8 Pharmacyclics LLC. *IMBRUVICA (ibrutinib) prescribing information*; 2022. https://www.imbruvica.com/files/prescribing-information.pdf. Accessed August 16, 2022.
9 AstraZeneca Pharmaceuticals Inc. *CALQUENCE (acalabrutinib) product information*; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. Accessed August 31, 2022.
10 BeiGene USA Inc. *BRUKINSA (zanubrutinib) product information*; 2019. https://www.brukinsa.com/prescribing-information.pdf. Accessed August 31, 2022.
11 Lilly USA. *JAYPIRCA (pirtobrutinib) prescribing information*; 2023. https://pi.lilly.com/us/jaypirca-uspi.pdf.
12 BeiGene Ireland Ltd. *REVLIMID (lenalidomide) EPAR*; 2022. https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf. Accessed August 31, 2022.
13 Celgene Corporation. *REVLIMID (lenalidomide) prescribing information*; 2019. https://packageinserts.bms.com/pi/pi_revlimid.pdf. Accessed August 16, 2022.
14 Takeda Pharmaceuticals. *VELCADE (bortezomib) prescribing information*; 2021. https://www.velcade.com/files/pdfs/VELCADE_PRESCRIBING_INFORMATION.pdf. Accessed August 31, 2022.
15 Pfizer Europe MA EEIG. *TORISEL (temsirolimus) EPAR product information*; 2022. https://www.ema.europa.eu/en/documents/product-information/torisel-epar-product-information_en.pdf. Accessed August 31, 2022.
16 Forero-Torres A, Ramchandren R, Yacoub A, et al. Parsaclisib, a potent and highly selective PI3Kdelta inhibitor, in patients with relapsed or refractory B-cell malignancies. *Blood*. 2019;133:1742–1752.
17 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.e3.
18 Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat Rev Cancer*. 2015;15:7–24.
19 Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kdelta inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood*. 2014;123:3398–3405.
20 Phillips TJ, Forero-Torres A, Sher T, et al. Phase 1 study of the PI3Kdelta inhibitor INCB040093 +/- JAK1 inhibitor itacitinib in relapsed/refractory B-cell lymphoma. *Blood*. 2018;132:293–306.
21 Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2017;35:3898–3905.
22 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.
23 Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370:1008–1018.
24 Shin N, Stubbs M, Koblish H, et al. Parsaclisib is a next-generation phosphoinositide 3-kinase delta inhibitor with reduced hepatotoxicity and potent antitumor and immunomodulatory activities in models of B-cell malignancy. *J Pharmacol Exp Ther*. 2020;374:211–222.
25 Yue EW, Li YL, Douty B, et al. INCB050465 (parsaclisib), a novel next-generation inhibitor of phosphoinositide 3-kinase delta (PI3Kdelta). *ACS Med Chem Lett*. 2019;10:1554–1560.
26 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.
27 Song Y, Zhou K, Zou D, et al. Safety and activity of the investigational bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) in patients with mantle cell lymphoma from a phase 2 trial. *Blood*. 2018;132(suppl 1):48.
28 Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126:739–745.
29 Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet*. 2018;391:659–667.
30 Phillips T, Avigdor A, Gurion R, et al. Efficacy and safety of parsaclisib in patients with relapsed or refractory marginal zone

lymphoma: primary analysis from a phase 2 study (CITADEL-204). *Blood*. 2021;138(suppl 1):44.
31 Lynch R, Avigdor A, McKinney MS, et al. Efficacy and safety of parsaclisib in patients with relapsed or refractory follicular lymphoma: primary analysis from a phase 2 study (CITADEL-203). *Blood*. 2021;138(suppl 1):813.
32 Zinzani PL, Martelli M, Ferrero S, et al. Use of BTK inhibitors with focus on ibrutinib in mantle cell lymphoma: an expert panel opinion statement. *Hematol Oncol*. 2022;40:518–527.
33 Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39:3441–3452.
34 Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. *Blood*. 2020;136:2038–2050.
35 Dong R, Yan Y, Zeng X, Lin N, Tan B. Ibrutinib-associated cardiotoxicity: from the pharmaceutical to the clinical. *Drug Des Devel Ther*. 2022;16:3225–3239.
36 Cohen JB, Shah NN, Alencar AJ, et al. MCL-133 pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in previously treated mantle cell lymphoma: updated results from the phase 1/2 BRUIN study. *Clin Lymphoma Myeloma Leuk*. 2022;22(Suppl 2): S394–S395.
37 Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397:892–901.
38 Globe Newswire. *TG Therapeutics announces voluntary withdrawal of the BLA/sNDA for U2 to treat patients with CLL and SLL*. 2022 [press release].
39 PRNewswire. *Secura Bio announces Copiktra® (duvelisib) strategic focus on T-cell lymphoma and voluntary U.S. withdrawal of the relapsed or refractory follicular lymphoma indication*. 2021 [press release].
40 Gilead. *Gilead statement on Zydelig® U.S. indication for follicular lymphoma and small lymphocytic leukemia*. 2022 [press release].
41 US Food and Drug Administration. *Phosphatidylinositol 3-kinase (PI3K) inhibitors in hematologic malignancies*; 2022. https://www.fda.gov/media/157762/download. Accessed August 16, 2022.