Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies

Running title: Parsaclisib for relapsed/refractory B-cell lymphoma

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Supplemental data

Supplemental text

Methods

Ex vivo pAKT assay

The ex vivo assay was performed by adding SUDHL-5 cells to patient whole blood and monitoring for changes in the level of pAKT. We examined the effect of parsaclisib on pAKT levels in this lymphoma cell line because these cells contain detectable levels of PI3Kδ that is constitutively active and cells are sensitive to parsaclisib for growth inhibition. Normal peripheral blood cells do not demonstrate measureable levels of pAKT. Parsaclisib inhibits pAKT levels in this whole blood assay in a dose-dependent fashion with an IC_{50} value of 4 nM and IC_{90} value of approximately 40 nM. In addition, PK analysis has demonstrated that parsaclisib distributes with body water and therefore it is expected that, at steady state, the drug level in the lymph node would be equivalent to the drug level in blood.

Protocol parts 4 and 5

Part 4 was a dose evaluation study of parsaclisib in combination with rituximab in patients with B-cell malignancies followed by expansion cohorts of patients with indolent follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Similarly, Part 5 was a dose evaluation study of parsaclisib in combination with rituximab and bendamustine in patients with B-cell malignancies, followed by an expansion cohort of patients with indolent FL. Both parts 4 and 5 were removed at a later protocol amendment due to the approval of obinutuzumab.

Additional patient exclusion criteria

Additional patient exclusion criteria included radiation treatment within 4 weeks, investigational study drug within 28 days (or 5 half-lives, whichever is longer), approved anticancer drugs (except steroids at ≤10 mg prednisone daily) within 21 (42 for nitrosoureas) days (or 5 half-lives, whichever is longer), unresolved toxicity grade ≥2, current or recent history of clinically meaningful infection, total bilirubin ≥1.2 × upper limit of normal (ULN), alkaline phosphatase ≥2.5 × ULN, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.0 × ULN, or creatinine clearance <50 mL/min based on Cockcroft-Gault formula.

Parsaclisib plus itacitinib/R-ICE combination dosing

For the parsaclisib plus itacitinib combination, dose escalation of parsaclisib proceeded using 3 + 3 design, starting with a parsaclisib dose approximately 25% less than the recommended dose determined for parsaclisib monotherapy. For each cohort, itacitinib was co-administered at a dose of 300 mg once daily.

For the parsaclisib plus rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) combination, dose escalation of parsaclisib proceeded using 3 + 3 design with a starting dose approximately 25% below the recommended dose determined for parsaclisib. R-ICE chemotherapy components were administered either according to institutional practice or per protocol. Per protocol, R-ICE was administered in 3 21-day cycles, according to the following schedule: rituximab 375 mg/m^2 on days 1 and 2 of cycle 1, and day 1 of cycles 2 and 3; ifosfamide 5000 mg/m^2 by continuous intravenous (IV) infusion over 24 hours on day 3 of each cycle; carboplatin (area under the curve

= 5 mg/mL; maximum dose 800 mg) by IV infusion on day 3; etoposide 100 mg/m^2 by IV on days 3 to 5.

Supplemental tables

Table S1. Definition of dose-limiting toxicity

Nonhematologic • ≥Grade 3 nonhematologic toxicity, excluding nausea, vomiting, and diarrhea • ≥Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/antidiarrheal therapy lasting >48 hours • Any toxicity considered a DLT in the opinion of the investigator and medical monitor
Hematologic • Grade 4 neutropenia lasting ≥7 days* • Febrile neutropenia (ANC $<1.0 \times 10^9$/L) with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour • Grade 3 thrombocytopenia associated with clinically significant bleeding (clinically significant as determined by the investigator or resulting in the need for a transfusion of red blood cells) • Grade 4 thrombocytopenia lasting >7 days • Grade 4 anemia
General • Any specific AE that results in a dose delay or reduction in more than one-third of patients

AE, adverse event; ANC, absolute neutrophil count; DLT, dose-limiting toxicity.

*Itacitinib can cause transient decreases in white blood cells due to margination; therefore, DLT rules required neutropenia to persist after holding itacitinib for 2 to 3 days. Where the clinical status of the patient allows, investigators were encouraged to wait 24 hours before starting

growth factors, to determine if white blood cell margination was contributing to the degree of neutropenia.

Table S2. Key study assessments

		Treatment					Follow-up
		Cycle 1			Other cycles		
	Screening Days –30 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	EOT	EOT +30 to +37 days
Prior/concomitant medications	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
12-lead ECG	X	X		X	X	X	X
Laboratory tests	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X
CT/MRI	X				X[*]	X	
FDG-PET	X				X[*†]	X	

Bone marrow examination	X				X[‡]		
Review AEs	X	X	X	X	X	X	X
Serum chemistry/hematology	X	X	X	X	X	X	X
Blood PK sample		X	X[§]	X	X[§‖]		
Blood PD sample		X		X	X[¶]		
Tumor tissue sample	X[#]				X[**]	X[**]	

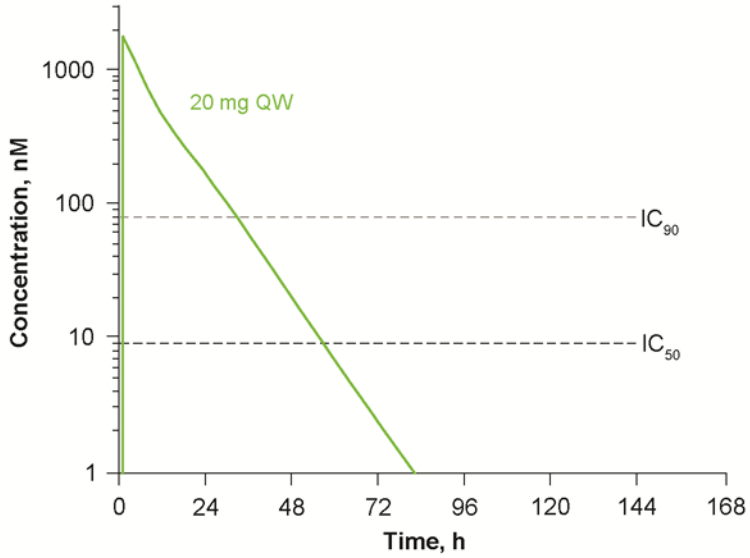
CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; FDG-PET, fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging; PD, pharmacodynamic; PK, pharmacokinetic.

*Every 9 weeks (3 cycles) or at a frequency consistent with the standard of care; performed only if measurable disease is present. [†]May be performed per standard of care; applicable for lymphomas only. [‡]To confirm a CR. [§]Not collected from patients receiving parsaclisib plus R-ICE. [‖]Cycle 2 only; collected from patients with B-cell malignancies in the parsaclisib monotherapy expansion cohort (cohort A). [¶]Through cycle 6 for parsaclisib monotherapy and parsaclisib plus itacitinib combination, and in cycles 3, 6, 9, and 12 for parsaclisib plus R-ICE combination. [#]Archival tissue acceptable; for patients with CLL, peripheral blood acceptable. [**]Optional on-treatment or EOT biopsy (or peripheral blood for patients with CLL).

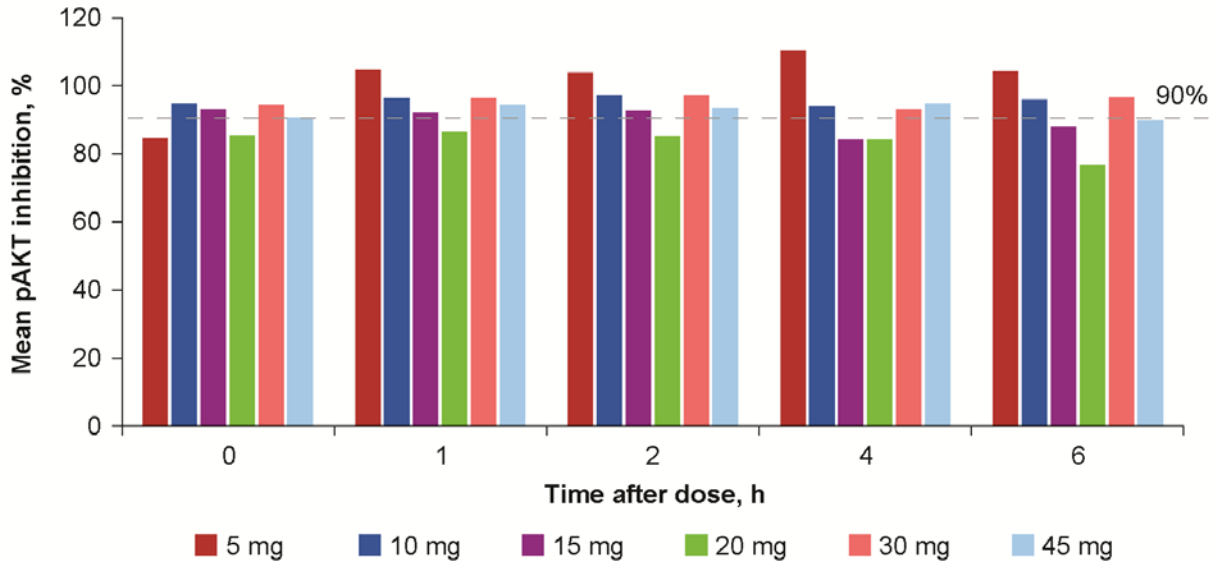
Supplemental figures

Supplemental Figure S1. Simulated pharmacokinetics for parsaclisib 20 mg dosed weekly.

QW, once weekly.

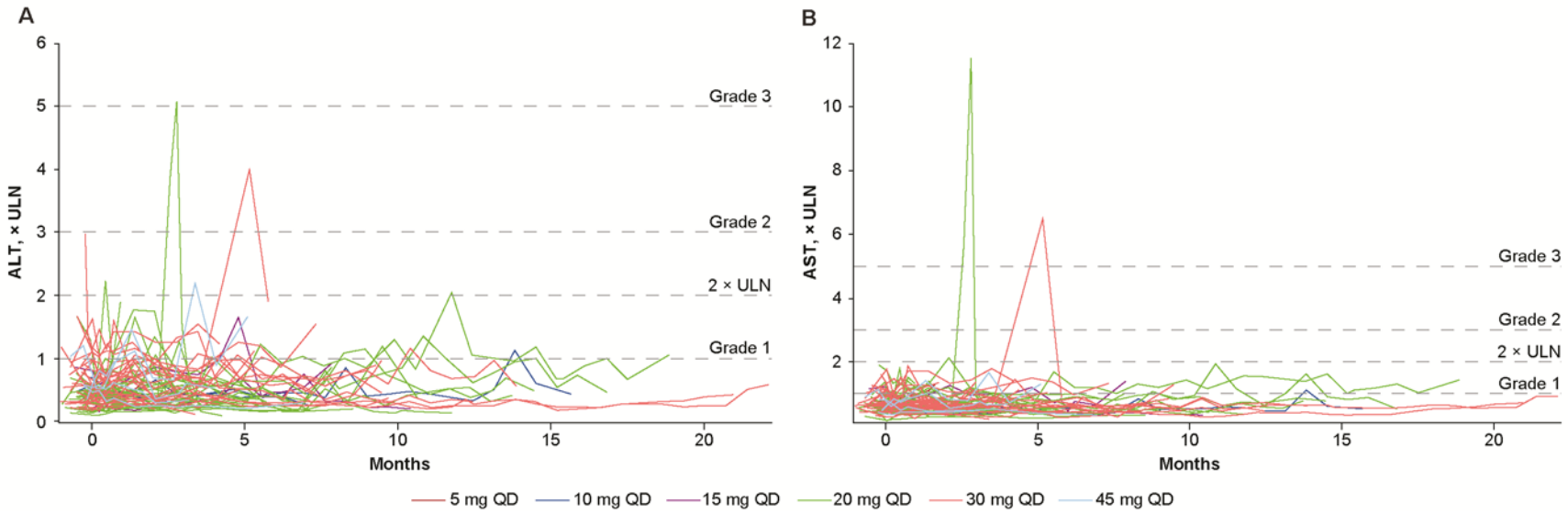


Supplemental Figure S2. Mean percent inhibition of pAKT at steady state. Parsaclisib was dosed once daily, and levels of phosphorylated AKT (pAKT; Ser473) were measured by flow cytometry in SU-DHL cells added to patient whole blood before and after parsaclisib treatment on day 15 of cycle 1. Time 0 represents the trough measurement from Day 14.



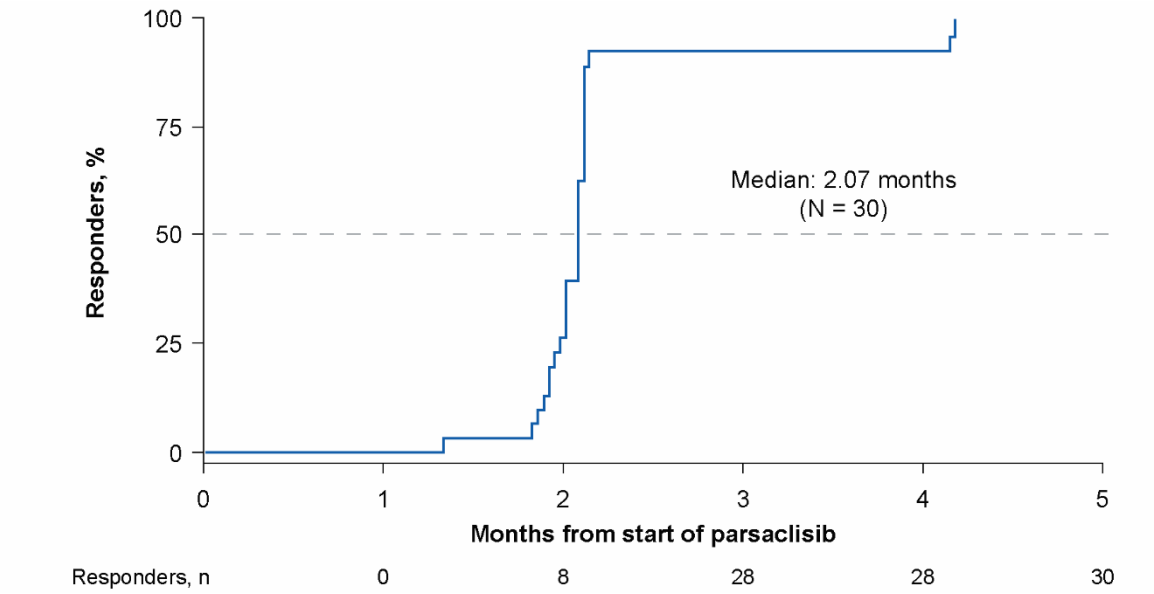
Supplemental Figure S3. (A) ALT and (B) AST over time in patients receiving parsaclisib monotherapy.

QD, once daily.



Supplemental Figure S4. Monotherapy time to response among NHL subtypes of interest (DLBCL, FL, MCL, MZL).

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma.



Supplemental Figure S5. Pharmacokinetics of parsaclisib in combination with itacitinib or R-ICE. (A) Cycle 1 day 1. (B) Cycle 1 day 15.

IC_{50}, half maximal inhibitory concentration; IC_{90}, 90% maximal inhibitory concentration.