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Phase I study of ON 01910.Na (Rigosertib), a multikinase PI3K inhibitor in relapsed/refractory B-cell malignancies

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Chronic lymphocytic leukemia (CLL) and mantle cell lymphoma lymphoma (MCL) are incurable B-cell malignancies usually responsive to initial immunochemotherapy but virtually all patients experience relapse. Salvage therapy choices for relapsed/refractory disease are often limited by resultant cytopenias and acquired drug resistance. The current priority in these B-cell malignancies, therefore, is to develop agents with novel mechanisms of action that are selective for tumor cells, overcome shared patterns of acquired drug resistance, and exhibit limited toxicities.

Styrylbenzylsulfones are a new family of non-ATP-competitive anti-cancer agents that induce apoptosis in a variety of tumor cell lines including those resistant to many chemotherapy agents.[1,2] As a class, styrylbenzylsulfones inhibit cell cycle progression and induce mitotic arrest of tumor cells with less toxicity to normal human cells.[3,4] ON 01910.Na (rigosertib) is a styryl sulfonyl compound that demonstrated inhibition of phosphatidylinositol-3-kinase (PI3K), preferentially targeting the PI3Kα and PI3Kβ isoforms, and triggered apoptosis via the release of cytochrome *c* from mitochondria in MCL cell lines.[3] Rigosertib's mechanism of action was initially considered to include inhibition of polo-like 1 kinase (PLK-1),[4] but evidence for direct inhibition was not confirmed in subsequent studies[5] and its anti-mitotic activity may rely on the phosphorylation of mitosis coordinator RanGAP1·SUMO1.[6] First-in-man studies of rigosertib in solid tumors demonstrated excellent tolerability with limited hematologic toxicity.[7] Rigosertib has also demonstrated pre-clinical and early clinical activity in myelodysplastic syndromes (MDS)[8,9] and it is currently being tested in a randomized phase III trial in patients with relapsed/refractory MDS [NCT01241500].

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CONFLICT OF INTEREST DISCLOSURE

Francois Wilhelm is Chief Medical Officer and Senior Vice President at Onconova Therapeutics Inc. The other co-authors declare no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

The design of this scientific work was done by MR and AW. MR, MF, GA, and AW were responsible for care of all patients. Data analysis was done by MR, FW and AW. The manuscript was written by MR and AW and submitted after critical review by all authors.

We have previously reported that rigosertib induces rapid apoptosis in CLL cells with the relative sparing of normal B-cells and T-cells.[10] We demonstrated that the in vitro activity of rigosertib involved a dual mechanism of inhibition of PI3K pathway signaling coupled with the induction of an oxidative stress response. Importantly, activity of rigosertib was equally observed against CLL cells with adverse prognostic features such as unmutated immunoglobulin heavy-chain variable regions and the loss of *TP53.* These preclinical data prompted our exploration of rigosertib in lymphoid malignancies. In this letter, we report the safety and clinical toxicity profile of rigosertib in patients with relapsed and refractory CLL, MCL and related B-cell lymphoid malignancies.

Adult patients aged ≥ 18 with CLL, MCL, hairy cell leukemia (HCL), and multiple myeloma (MM) refractory or relapsed after ≥ 1 lines of therapy were eligible. Patients had measurable disease and were ineligible for, or opted not to participate in alternative treatment options such as allogeneic transplantation. Exclusion criteria included systemic therapy (steroids permitted) within 4 weeks of enrollment, Eastern Cooperative Oncology Group performance of ≥3, human immunodeficiency virus (HIV) infection on anti-retroviral therapy, glomerular filtration rate (GFR) < 40ml/min, serum sodium < 134meq/L, and the presence of active ascitic or pleural fluid (the latter exclusion criteria were based on preliminary reports of hyponatremia in patients with solid tumors treated with rigosertib). Patients with pre-existing cytopenias were eligible if their baseline absolute neutrophil count was ≥ 500 cells/μL and if their platelet count could be maintained above 10,000 μ/L with transfusion. There was no limit on previous numbers of regimens and patients who had previously been treated with autologous or allogenetic stem cell transplantation were eligible. All research was approved by the Institutional Review Board of the National, Heart, Lung, and Blood Institute (NHLBI), and the study was conducted in accordance with the Declaration of Helsinki. Treatment responses were determined by the investigator using the updated International Workshop on Chronic Lymphocytic Leukemia (IWCLL) response criteria for CLL,[11] the International Myeloma Working Group response criteria for MM,[12] and the revised Cheson response criteria for MCL.[13] For HCL complete response (CR) required absence of HCL cells in blood and bone marrow; no hepatosplenomegaly; and resolution of blood counts to neutrophils ≥ 1,500/μL, platelets ≥ 100,000/μL, and hemoglobin (Hgb) ≥ 11 g/dL in women and ≥ 12 g/dL in men; partial remission (PR) required ≥ 50% reduction in abnormal blood lymphocyte count, ≥ 50% reduction of lymphadenopathy, ≥ 50% reduction in abnormal hepatosplenomegaly and achievement of ≥ 50% improvement over baseline in normal blood counts; PD was defined as ≥ 25% increase in adenopathy or appearance of new lymphadenopathy, ≥ 25% increase in liver or spleen measured below the costal margin, ≥ 25% decrease in normal blood counts, or a ≥ 25% increase in circulating abnormal lymphocytes; stable disease was defined as lack of CR, PR, or PD.

Rigosertib was administered intravenously via an ambulatory infusion pump every 14 days across 5 cohorts in escalating doses. A standard phase 1 dose-escalation (3+3) design was used. The first three cohorts received rigosertib according to body-surface area calculations over 48 hours in escalating doses of 1500mg/m2/day x 2 days, 1800mg/m2/day x 2 days, and 2100mg/m2/day x 2 days. The protocol was amended to flat dosing for cohorts 4 and 5

based on information that infusions over 72 hours were more effective in MDS (unpublished data). Thus, cohort 4 and 5 received flat dosing of rigosertib at 1800mg/day x 3 days (the dose currently being studied in the phase III study in patients with MDS) and 2100mg/day x 3 days (Table 1). Dose-limiting toxicity (DLT) was defined as any G3 or higher non-hematologic toxicity that was not readily reversible and G3 or higher hematologic toxicities that did not resolve in 14 days occurring in the first 2 cycles of therapy. The primary endpoint of the study was to determine the toxicity profile (including the maximum tolerated dose and recommended phase 2 dose) of rigosertib after 2 cycles. A dose escalation beyond cohort 5 was not considered due to previous reports of dose limiting toxicities in patients with acute myeloid leukemia or myelodysplastic syndrome treated at higher doses or with extended infusion duration (unpublished data). All patients were allowed to continue past the primary endpoint to day 56 (4 cycles infused) to determine early clinical activity of rigosertib.

A total of 16 patients with relapsed CLL (10), MCL (2), MM (2), and HCL (2) were enrolled (Table 1). Median age of the patients was 61 years (range 52–65) and 10 of the 16 patients (63%) were of male gender. Over 30% of patients had pre-existing ANC counts < 1000 cells/μL, and the median number of prior regimens was 4 (range 2–9). Overall, toxicities were minimal and almost exclusively ≤ G2 (Table 2). The most common reported toxicities include musculoskeletal pain, nausea, constipation, and diarrhea. Two cases of venous thrombosis associated with peripherally inserted central catheters (PICC) were observed. Non-hematologic grade 3/4 drug-related adverse events included 1 case of syncope that did not recur upon subsequent dosing and 1 case of elevated alanine aminotransferase (ALT) that resolved without intervention. There was 1 cardiac death in a patient with pre-existing heart disease that was classified as unrelated to study drug. Grade 3/4 hematologic toxicity occurred exclusively in patients with pre-existing cytopenias. One case of neutropenia occurred in a patient in cohort 3 with relapsed MM who had progressive bone marrow infiltration and resulted in discontinuation of protocol therapy. The other 6 cases of ≥ G3 neutropenia occurred in 2 patients in cohort 5 that both had pre-existing G2 neutropenia. No DLTs were recorded and no patient discontinued study drug due to toxicity.

Fourteen of the 16 patients were evaluable for secondary endpoints including objective response or signs of early biologic activity such as reduction in tumor burden or tumor markers (Table 1). Two patients were considered not evaluable for response: one patient with MM was unable to continue after only 1 cycle of therapy due to neutropenia and the other patient with MM did not continue past cycle 2 due to rising light chains that did not meet criteria for progressive disease (PD). No cases of early clinical activity were noted and no patient continued past 4 cycles of therapy. 7/14 patients (50%) had stable disease (SD) and 7/14 (50%) had PD.

We conclude that escalating doses of the multikinase inhibitor rigosertib are well-tolerated in patients with relapsed/refractory B-cell malignancies and associated with a relative lack of hematologic toxicity. Our schedule tested doses higher than that currently in phase III testing in MDS patients and was associated with minimal toxicity. Heavily pre-treated patients with pre-existing cytopenias tolerated rigosertib without an increased risk of infection or significant worsening of blood counts. Despite the encouraging preclinical

activity, no significant clinical activity was observed with rigosertib as a single agent in these B-cell malignancies. Further development of rigosertib for lymphoid malignancies will require either combination therapy[14] or alternative dosing schedules.

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Table I

Patient characteristics and response

Study number	Gender/Age (y)	Disease	# of prior regimens	Baseline ANC	Dosing schedule	# of cycles completed	Response	Reason for discontinuation
01	M/58	HCL	4	850	1200mg/m2 over 48 h	4	SD	CT
02	M/52	CLL	6	2430	1200mg/m2 over 48 h	4	SD	CT
03	M/64	MM	9	1540	1200mg/m2 over 48 h	2	NE	WC
04	M/66	HCL	6	1080	1500mg/m2 over 48 h	4	SD	CT
05	M/55	CLL	5	1010	1500mg/m2 over 48 h	4	PD	CT
06	M/67	MCL	4	4440	1500mg/m2 over 48 h	1	NE	Death
07	F/65	CLL	2	1850	1500mg/m2 over 48 h	3	PD	PD
08	F/65	CLL	4	670	1800mg/m2 over 48 h	4	SD	CT
09	F/61	MM	6	620	1800mg/m2 over 48 h	1	PD	PD
10	F/65	CLL	2	650	1800mg/m2 over 48 h	1	PD	PD
11	M/60	MCL	7	1280	1800mg over 72 h	3	PD	PD
12	F/65	CLL	4	4150	1800mg over 72 h	4	SD	CT
13	M/52	CLL	2	4110	1800mg over 72 h	4	SD	CT
14	M/58	CLL	6	1730	2100mg over 72 h	4	PD	CT
15	F/61	CLL	4	1200	2100mg over 72 h	4	SD	CT
16	M/57	CLL	3	670	2100mg over 72 h	4	PD	CT

HCL: hairy cell leukemia; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; ANC: absolute neutrophil count in cells/μL; SD: stable disease; NE: not evaluable for response; PD: progression of disease; CT: completed therapy as planned; WC: withdrew consent;

Table 2

Grade 2 and above treatment-related adverse events during Cycles 1 and 2 (n=16)

Adverse Events	Cohort 1 (n=3)		Cohort 2 (n=4)		Cohort 3 (n=3)		Cohort 4 (n=3)		Cohort 5 (n=3)		Total	
	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4	G2	G3/4
Hematologic												
Neutropenia	-	-	-	-	-	1	-	-	-	6	-	7
Anemia	-	-	-	-	-	-	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	-	-	-	-	-	-	-
Non-Hematologic												
Syncope	-	-	-	-	-	-	1	-	-	-	-	1
Constipation	-	-	-	-	-	-	-	-	1	-	1	-
Musculoskeletal pain	-	-	-	-	-	-	-	-	1	-	1	-
Infection	-	-	1	-	1	-	-	-	-	-	2	-
Catheter-related thrombosis	-	-	2	-	-	-	-	-	-	-	2	-
ALT increased	-	-	-	-	-	-	-	-	-	1	-	1

2 events of G4 neutropenia were observed in a cohort 5 in patient with pre-existing G3 neutropenia. 4 events of G3 neutropenia were observed in cohort 5 in patient with pre-existing G2 neutropenia. All events were felt possibly due to drug and possibly due to disease