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An Open-label, Phase II Trial of Entospletinib (GS-9973), a Selective Spleen Tyrosine Kinase Inhibitor, in Diffuse Large B-cell Lymphoma

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Abstract

In an open-label, phase II study, we evaluated entospletinib monotherapy for patients with relapsed or refractory diffuse large B-cell lymphoma. Entospletinib had limited activity in these patients. Seventy-four percent of the patients experienced a grade ≥ 3 adverse event. Treatment was interrupted in 42% of the patients, and the drug was discontinued in 19% of the patients.

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Disclosure

J.M.B. has consulted and served on the board of directors/advisory committee for Incyte Corporation, Celgene, Bayer, Genentech, Inc, and Gilead Sciences, Inc. A.S. has consulted for, and received honoraria from, Bristol-Myers Squibb and consulted for, given paid testimony for, and conducted research funded by, SPECTRUM Pharmaceuticals, Inc. J.E. is a current or former employee of OHC and has consulted for Jazz Pharmaceuticals PLC. D.P.D. has consulted and served on the board of directors/advisory committee for Juno Therapeutics. W.Y. is a current or former employee of and has owned stock or held ownership interests in Gilead Sciences, Inc. W.S. is a current or former employee of, has conducted research for, and has owned stock or held ownership interests in Gilead Sciences, Inc. S.A. has consulted for Roche Canada Pharmaceuticals and Lundbeck Inc; conducted research projects funded by Epizyme, Genentech, Inc, Gilead Sciences, Inc, Takeda Pharmaceutical Company, Novartis AG, and AbbVie; received honoraria from Janssen, Roche Pharmaceuticals, Lundbeck Inc, and Novartis AG; and served on the board of directors/advisory committee for Knight Therapeutics Inc. J.P.S. is a current or former employee of US Oncology, Inc, and has consulted and conducted research for Gilead Sciences, Inc, Genentech, Inc, Pharmacyclics LLC, AbbVie Inc, TG Therapeutics, Inc, and Seattle Genetics. The remaining authors declare that they have no competing interests.

Background: Entospletinib (GS-9973) is an oral, selective inhibitor of spleen tyrosine kinase. Entospletinib monotherapy was evaluated in a multicenter, phase II study of subjects with relapsed or refractory B-cell malignancy.

Patients and Methods: The study included 43 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The participants received 800 mg of the original, monomesylate formulation of entospletinib twice daily as a starting dose; the doses could be reduced because of toxicity throughout the study.

Results: No patient achieved a complete or partial response, 5 patients (12%) had stable disease, and 26 patients (60%) had progressive disease. Progression-free survival (PFS) at 16 weeks was 3.6% (95% confidence interval [CI], 0.3%−15.3%), and the median PFS was1.5 months (95% CI, 1–1.7 months). The independent review committee—assessed nodal response for 27 evaluable patients showed a reduced tumor burden in 6 patients (22%). The median duration of entospletinib treatment for these 6 patients was 9 weeks (range, 3–24 weeks). One patient (4%) had a decrease of > 50% in the sum of the product of the nodal diameters. The treatment-emergent adverse events occurring in ≥ 20% of the cohort were fatigue, nausea, decreased appetite, constipation, dyspnea, diarrhea, dehydration, cough, insomnia, and peripheral edema. The common laboratory abnormalities occurring in ≥ 20% of the subjects were lymphocytopenia, anemia, creatinine (chronic kidney disease), increased aspartate aminotransferase, hypoalbuminemia, total bilirubin, hyponatremia, leukopenia, increased alanine aminotransferase, increased alkaline phosphatase, and hyperglycemia.

Conclusion: Entospletinib monotherapy at 800 mg twice daily demonstrated limited activity in patients with advanced, relapsed DLBCL.

Keywords

B-cell receptor signaling inhibitors; DLBCL; Hematologic malignancies; Monotherapy; Syk

Spleen tyrosine kinase (Syk) is a cytoplasmic protein tyrosine kinase that acts as a proximal intermediary in the B-cell receptor (BCR)-signaling pathway.[1–3] Syk is predominantly expressed in cells of hematopoietic lineage and functions in conjunction with activated immunoreceptors to regulate downstream signaling pathways. Syk signaling elicits a range of diverse biologic functions, including cellular development, function, proliferation, migration, and survival.[4–7] These findings have implicated Syk and the BCR pathway as essential for cell proliferation and survival in multiple B-cell malignancies.[8]

Entospletinib (GS-9973) is an adenosine triphosphate competitive inhibitor of Syk with high selectivity (dissociation constant, 7.6 nM) in a broad kinase panel screening. A dose-finding study of healthy volunteers determined the recommended phase II dose of 800 mg twice daily.[9] Clinical trials have shown fewer off-target adverse events (AEs) than were previously observed with an alternate Syk inhibitor, fostamatinib, which is less selective than entospletinib.[9,10]

The safety, tolerability, and efficacy of entospletinib were evaluated in a single-agent, open-label, multicenter phase II trial that enrolled 5 separate cohorts of subjects with relapsed or refractory hematologic malignancies, including chronic lymphocytic leukemia (CLL),

follicular lymphoma, other indolent non-Hodgkin lymphomas (iNHLs; including lymphoplasmacytic lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma), mantle-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL; ClinicalTrials.gov identifier, NCT01799889). The results from the CLL cohort have been reported previously.[11] We report the efficacy, safety, and tolerability of entospletinib as a single agent in the cohort of subjects with relapsed or refractory DLBCL.

Patients and Methods

Forty-three patients with previously treated DLBCL received ≥ 1 starting 800-mg dose of the original monomesylate formulation of entospletinib orally twice daily. The dose of entospletinib could be reduced as needed because of toxicities. The primary endpoint was progression-free survival (PFS) rate at 16 weeks. The secondary endpoints included evaluation of safety, objective response rate, duration of response, and time to response. Tumor imaging was performed at weeks 8, 16, and 24 and then every 12 weeks. The tumor response was assessed using the Cheson 2007 criteria.[12] An independent review committee assessed the primary and secondary efficacy endpoints. The futility assessment began when the first 10 subjects' outcomes in each DLBCL subtype (germinal center B-cell [GCB], non-GCB, or undetermined) became available. The relevant institutional review boards approved the study protocol, amendments, informed consent according to the Declaration of Helsinki, and other information that required preapproval. A more detailed description of the methods has been previously reported.[11]

Results

Patient Characteristics and Disposition

The patient characteristics are listed in Table 1. For the 43 patients with DLBCL, the median age was 68 years (range, 27–89 years), and 65% were male. The median number of previous treatment regimens was 2 (range, 1–7). Of the 43 patients, 79% had Ann Arbor stage III-IV disease at entry into the study. As described by the local pathologists using immunohistochemistry algorithms to classify the cell of origin, 42% had GCB, 39% had non-GCB, and 19% had an undetermined or a missing subtype. Previous therapies included rituximab in 98%, alkylating agents in 95%, bendamus-tine in 19%, and anthracyclines in 86%. The most common reasons for discontinuation of the study drug were progressive disease (56%) and AEs (19%; Table 1). As of June 2, 2016, all patients had discontinued treatment with entospletinib, with a median duration of treatment of 1 month.

Safety

The AEs experienced by the DLBCL patients treated with entospletinib are listed in Table 2. Of the 43 patients, 42 (98%) experienced an AE, of whom 32 patients (74%) experienced grade ≥ 3 AEs; 13 patients (30%) had grade ≥ 3 AEs related to entospletinib. Serious AEs occurred in 16 patients (37%). Treatment was interrupted in 18 patients (42%) and discontinued in 8 patients (19%) because of AEs. One patient had an AE leading to dose reduction, and 4 patients (9%) experienced an AE that led to death. Ten patients died in the study within 30 days from the last dose of the study drug: 7 patients (16.3%) died of

progressive disease and 3 (7%) of causes (septic shock, acidosis, and respiratory failure for 1 each) judged by the investigator as not related to the study drug (Table 1).

Efficacy

Of the 43 patients treated with entospletinib, none achieved a complete or partial response, although 5 (12%) had stable disease. Of the 43 patients, 26 (61%) had progressive disease, 1 (2%) was not evaluable, and 11 (26%) had discontinued the study without undergoing any assessments. The rate of PFS at 16 weeks was 3.6% (95% CI, 0.3%−15.3%). The median PFS was 1.5 months (95% CI, 1.1–1.7 months; Figure 1). The independent review committee-assessed nodal response for the 29 patients with an evaluable sum of the product of the diameters demonstrated that tumor burden was reduced in 6 patients (21%). The median duration of entospletinib treatment for these 6 patients was 9 weeks (range, 3–24 weeks). One patient (3%) had a decrease of ≥ 50% in sum of the product of the diameter (Figure 2).

Discussion

Targeted inhibition of the BCR signaling pathway, which involves key signaling enzymes such as Syk, Bruton's tyrosine kinase, and phosphatidylinositol 3-kinase-δ, is a strategic therapeutic approach across hematologic malignancies.[12,13]

In the present study, entospletinib monotherapy at 800 mg twice daily demonstrated no significant activity in patients with advanced, relapsed DLBCL. A previous phase II trial of fostamatinib (Rigel Pharmaceuticals), another Syk inhibitor, also demonstrated a relatively low response rate (22%) in 23 patients with relapsed DLBCL.[7] The lack of activity of Syk inhibition in patients with relapsed DLBCL is in contrast to what would have been expected from preclinical data.[14–18]

The safety profile of entospletinib in the DLBCL subgroup of the present study was similar to that observed in other cohorts of the study. In the DLBCL, CLL, and iNHL cohorts, the rates of treatment interruption due to AEs were 42%, 45%, and 54%, respectively. The rates of treatment discontinuation due to AEs in the DLBCL, CLL, and iNHL cohorts were 19%, 17%, and 15%, respectively. AEs leading to death occurred in 9%, 2%, and 4% of patients in the DLBCL, CLL, and iNHL cohorts, respectively.

Although it is unclear why entospletinib monotherapy lacked activity in the present study, it is possible that resistance to Syk inhibition played a role. Potential mechanisms of resistance of DLBCL to Syk inhibition include transcriptional upregulation of Syk mediated by FOXO1 and PTEN depletion.[19] However, data have suggested that Syk inhibition combined with BCL2 inhibitors might be a rational approach to overcoming this resistance.[19–22] High levels of Mcl-1, which can be produced by sustained stimulation of the BCR, confer resistance to BCL2 inhibitors.[19–21] Studies by Bojarczuk et al[22] have demonstrated that Syk inhibitors prevent BCR-mediated Mcl-1 induction more effectively than do Bruton's tyrosine kinase or PI3Kδ inhibitors, suggesting that Syk inhibition combined with BCL inhibitors might be more effective than either one alone or combined with other agents in treating B-cell malignancies.[22]

Combining Syk inhibition with Janus kinase (JAK)1/3 inhibition could be another rational approach. It has been demonstrated that interleukin-4 can protect cells from the apoptosis mediated by ibrutinib and idelalisib and that such protection could be reversed by JAK1/3 inhibition.[23] Pure Syk inhibition with P505–15 did not inhibit the phosphorylation of STAT6 that follows exposure to interleukin-4; however, inhibition of JAK1/3 with either the JAK3 inhibitor tofacitinib or with the dual Syk-JAK inhibitor cerdulatinib inhibited signaling mediated by phosphorylated STAT6.[24] The same group also demonstrated synergism between cerdulatinib and the BCL2 inhibitor venetoclax.[24] How these results will translate into effectiveness in patients, especially those with DLBCL, remains to be determined.

Additional preclinical data have demonstrated that although entospletinib inhibited cell proliferation and induced apoptosis in DLBCL cell lines, as a single agent it did not induce tumor regression in a xenograft model.[25] However, significant synergy appeared to be present when an adequate dose of entospletinib was combined with vincristine, leading to tumor regression.[25] Future clinical trials are needed to evaluate the efficacy of entospletinib in combination therapy.

Conclusion

Entospletinib monotherapy at 800 mg twice daily demonstrated limited activity in patients with relapsed or refractory DLBCL. Although the rate of grade 3/4 AEs was relatively high, we believe that most of the AEs resulted from disease progression rather than the study drug. Based on results of the predinical data, the efficacy of entospletinib in combination will be evaluated in future clinical trials.

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Clinical Practice Points

- Single-agent entospletinib was not effective in patients with relapsed DLBCL.
- Preclinical data have suggested potential synergy of combining Syk inhibitors with vinca alkaloids, JAK1/3 inhibitors, and BCL2 inhibitors.

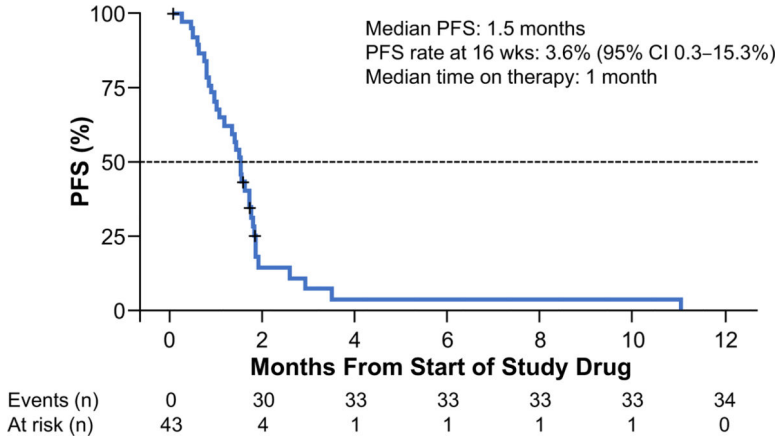

Figure 1.

Independent Review Committee–Assessed Progression-Free Survival (PFS). The Median PFS Was 1.5 Months. The Rate of PFS at 16 Weeks Was 3.6% (95% Confidence Interval [CI], 0.3%–15.3%). The Median Therapy Duration Was 1 Month

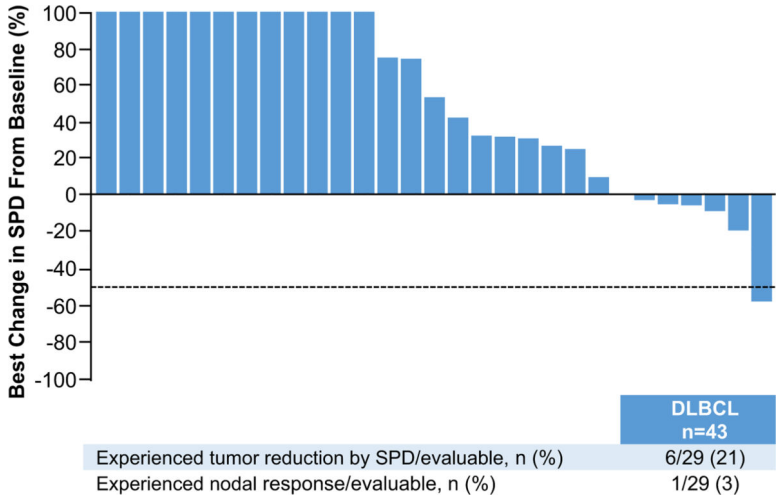

Figure 2.

Independent Review Committee–Assessed Changes in the Measured Size of Lymph Nodes From Baseline in Subjects With Diffuse Large B-Cell Lymphoma (DLBCL). Of the 43 Patients in the Cohort, 6 of 29 Evaluable Patients (21%) Experienced Tumor Reduction by Sum of Product of the Diameter (SPD) and 1 of 29 Evaluable Patients (3%) Experienced a Nodal Response. *Nodal Response Was Defined as ≥ 50% Decrease From Baseline in SPD

Table 1

Characteristics of Subjects With DLBCL at Baseline and Study Status (n = 43)

Characteristic	n (%)
Male gender	28 (65)
Age, y	
Median	68
Range	27–89
Previous therapies, n	
Median	2
Range	1–7
Anti-CD20 antibody	42 (98)
Rituximab	42 (98)
Any alkylating agent	41 (95)
Bendamustine	8 (19)
Anthracyclines	37 (86)
DLBCL subtype	
ABC	10 (23)
GCB	18 (42)
Other	
BCL6, MM1	1 (2)
Non-GCB	6 (14)
Undetermined or missing	8 (19)
Disposition and exposure	
Continued study drug	0
Exposure, wk	
Median	4
Range	1–52
Reason for discontinuing study drug	
PD	24 (56)
Death	3 (7)
AE	8 (19)
Investigator discretion	4 (9)
Noncompliance with study drug	1 (2)
Protocol-specified criteria for withdrawal	1 (2)
Withdrew consent	2 (5)

Abbreviations: ABC = activated B cell; AE = adverse event; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B cell; PD = progressive disease.

Table 2

Treatment-emergent Adverse Events Independent of Causality Occurring in ≥ 20% of Patients, Common Laboratory Abnormalities Occurring in ≥ 20% of Patients, and Serious Adverse Events Occurring in ≥ 3% of Patients

Variable	Any Grade, n (%)	Grade ≥ 3, n (%)
TEAEs in ≥ 20% of patients		
Fatigue	18 (42)	4 (9)
Nausea	18 (42)	3 (7)
Decreased appetite	16 (37)	1 (2)
Constipation	14 (33)	2 (5)
Dyspnea	13 (30)	3 (7)
Diarrhea	11 (26)	4 (9)
Dehydration	10 (23)	3 (7)
Cough	9 (21)	1 (2)
Insomnia	9 (21)	0
Peripheral edema	9 (21)	0
Common laboratory abnormalities in ≥ 20% of patients		
Lymphocytopenia	21 (49)	16 (37)
Anemia	20 (47)	4 (9)
Creatinine (chronic kidney disease)	19 (44)	1 (2)
Increased AST	16 (37)	4 (9)
Hypoalbuminemia	14 (33)	0
Total bilirubin	13 (30)	1 (2)
Hyponatremia	12 (28)	5 (12)
Leukopenia	11 (26)	1 (2)
Increased ALT	11 (26)	5 (12)
Alkaline phosphatase increased	9 (21)	0
Hyperglycemia	9 (21)	0
Serious AEs in ≥ 3% of patients		
Pneumonia	3 (7)	2 (5)
Dehydration	2 (5)	2 (5)
Dyspnea	2 (5)	1 (2)
Febrile neutropenia	2 (5)	2 (5)
Small intestinal obstruction	2 (5)	2 (5)

Abbreviations: AEs = adverse events; ALT = alanine transaminase; AST = aspartate transaminase; TEAEs = treatment-emergent AEs.