bjh research paper

An open-label phase 2 trial of entospletinib in indolent non-Hodgkin lymphoma and mantle cell lymphoma

David J. Andorsky,[1] Kathryn S. Kolibaba,[2] Sarit Assouline,[3] Andres Forero-Torres,[4] Vicky Jones,[5] Leonard M. Klein,[6] Dipti Patel-Donnelly,[7] Mitchell Smith,[8] Wei Ye,[9] Wen Shi,[9] Christopher A. Yasenchak[10] and Jeff P. Sharman[10]

[1]*Rocky Mountain Cancer Centers/The US Oncology Network, Boulder, CO,* [2]*Compass Oncology/The US Oncology Network, Vancouver, WA, USA,* [3]*Gerald Bronfman Centre, McGill University, Montreal, QC, Canada,* [4]*University of Alabama at Birmingham School of Medicine, Birmingham, AL,* [5]*North Star Lodge Cancer Center, Yakima, WA,* [6]*Illinois Cancer Specialists/The US Oncology Network, Niles, IL,* [7]*Virginia Cancer Specialists/The US Oncology Network, Fairfax, VA,* [8]*School of Medicine & Health Sciences, The George Washington University, Washington, DC,* [9]*Gilead Sciences, Inc., Foster City, CA, and* [10]*Willamette Valley Cancer Institute and Research Center/The US Oncology Network, Eugene, OR, USA*

Received 4 April 2018; accepted for publication 29 June 2018

Correspondence: David J. Andorsky, MD, Rocky Mountain Cancer Centers, 4715 Arapahoe Avenue, Boulder, CO 80303, USA.
E-mail: David.Andorsky@usoncology.com

Summary

Spleen tyrosine kinase (Syk) mediates B-cell receptor signalling in normal and malignant B cells. Entospletinib is an oral, selective Syk inhibitor. Entospletinib monotherapy was evaluated in a multicentre, phase 2 study of patients with relapsed or refractory indolent non-Hodgkin lymphoma or mantle cell lymphoma (MCL). Subjects received 800 mg entospletinib twice daily. Forty-one follicular lymphoma (FL), 17 lymphoplasmacytoid lymphoma/Waldenström macroglobulinaemia (LPL/WM), 17 marginal zone lymphoma (MZL) and 39 MCL patients were evaluated. The primary endpoint was a progression-free survival (PFS) rate (defined as not experiencing progression or death) at 16 weeks for patients with MCL and at 24 weeks for patients with FL, LPL/WM and MZL. The most common treatment-emergent adverse events were fatigue, nausea, diarrhoea, vomiting, headache and cough. Common laboratory abnormalities were anaemia, neutropenia and thrombocytopenia; aspartate transaminase, alanine transaminase, total bilirubin and serum creatinine were all increased. PFS at 16 weeks in the MCL cohort was 63·9% [95% confidence interval (CI) 45–77·8%]; PFS at 24 weeks in the FL, LPL/WM, MCL and MZL cohorts was 51·5% (95% CI 32·8–67·4%), 69·8% (95% CI 31·8–89·4%), 56·6% (95% CI 37·5–71·8%) and 46·2% (95% CI 18·5–70·2%), respectively. Entospletinib had limited single-agent activity with manageable toxicity in these patient populations.

Keywords: B-cell receptor signalling inhibitors, indolent non-Hodgkin lymphoma, mantle cell lymphoma, entospletinib, spleen tyrosine kinase inhibitors.

Spleen tyrosine kinase (Syk) is a cytoplasmic protein tyrosine kinase which acts upstream of both Bruton tyrosine kinase (BTK) and phosphoinositide3-kinase (PI3K) in the B-cell receptor (BCR) signalling pathway (Stevenson & Caligaris-Cappio, 2004; Kipps, 2007; Gobessi *et al*, 2009). Expression of Syk occurs predominantly in cells of the haematopoietic lineages. Phosphorylation of Syk creates docking sites for signalling proteins that activate BCR pathway signals. Syk signalling elicits a range of diverse biological functions, including cellular development, function, proliferation, migration and survival (Chiorazzi & Ferrarini, 2003; Quiroga *et al*, 2009; Buchner *et al*, 2010; Friedberg *et al*, 2010). These findings have implicated Syk and the BCR pathway as essential for proliferation, migration, and survival of lymphoma cells in a variety of B-cell malignancies, including lymphoplasmacytoid lymphoma/Waldenström macroglobulinaemia (LPL/WM), follicular lymphoma (FL), marginal zone lymphoma (MZL) and mantle cell lymphoma (MCL) (Fowler & Davis, 2013).

There remains a significant unmet need with regard to the treatment of relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) and MCL. FL is the most common subtype of iNHL, characterized by recurrent relapses and progressively shorter remissions (Anastasia & Rossi, 2016). A recent study found that approximately 20% of patients with FL who received first-line R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) progress within 2 years and have a poor prognosis (Casulo *et al*,

 British Journal of Haematology, 2019, **184,** 215–222
First published online 5 September 2018
doi: 10.1111/bjh.15552

2015). Despite recent advances in therapy for LPL/WM, including the approval of ibrutinib (Treon *et al*, 2015), complete responses (CRs) are rarely achieved. Finally, MCL is a rare subtype of NHL with an aggressive clinical course that usually responds to first-line chemotherapy but remains incurable with an overall poor prognosis (Williams *et al*, 2010; Fakhri & Kahl, 2017; Spurgeon *et al*, 2017).

Entospletinib (GS-9973) is a competitive inhibitor of Syk that has excellent selectivity (dissociation constant, K_d of 7·6 nmol/l) in a broad kinase panel screening without the off-target adverse events (AEs) observed with fostamatinib (Ramanathan *et al*, 2013; Currie *et al*, 2014; Sharman & Di Paolo, 2016). Entospletinib at BID dosing higher than 200 mg has demonstrated inhibition of Syk activity, as measured by CD63 expression and phospho-Syk, in healthy subjects (Ramanathan *et al*, 2013; Sharman & Di Paolo, 2016).

The safety, tolerability and efficacy of entospletinib was evaluated in a single-agent, open-label, multi-centre Phase 2 trial which enrolled separate cohorts of subjects with R/R haematological malignancies including chronic lymphocytic leukaemia (CLL), FL, other iNHL [including LPL/WM, small lymphocytic lymphoma (SLL) and MZL], MCL or diffuse large B-cell lymphoma (DLBCL) (NCT01799889). This article reports the safety, tolerability and efficacy of entospletinib as a single agent in cohorts of subjects with R/R iNHL (FL, LPL/WM or MZL) and MCL. The results from the CLL cohort have been previously published (Sharman *et al*, 2015).

Patients and methods

Patients with a diagnosis of B-cell iNHL [FL (grades 1, 2, 3a), MZL and LPL/WM] or MCL (mantle cell- nodal, diffuse or blastoid), based on World Health Organization criteria (Swerdlow *et al*, 2008) were included. Patients had to have performance status 0–1 and received 2 or more prior treatments with cytotoxic chemotherapy and an anti-CD20 monoclonal antibody or radioimmunotherapy. The presence of radiographically-measurable lymphadenopathy or extranodal lymphoid malignancy [defined as the presence of ≥1 lesion that measures ≥2·0 cm in the longest diameter and ≥1·0 cm in the longest perpendicular diameter as assessed by computed tomography (CT) or magnetic resonance imaging (MRI)] was required in patients with FL, MCL or MZL. Subjects with LPL/WM who did not have radiographically-measurable progressive disease were required to have a measurable monoclonal serum IgM on serum protein electrophoresis (SPEP) with lymphoplasmacytic marrow involvement. Key exclusion criteria included known transformation from iNHL to an aggressive form of NHL, known active central nervous system or leptomeningeal lymphoma and the presence of known intermediate- or high-grade myelodysplastic syndrome.

After informed consent, all patients received 800 mg of the original monomesylate formulation of entospletinib orally twice daily as the starting dose under fasting conditions for 28 days, which was considered as one cycle. Subjects were treated until progression of disease, unacceptable toxicity or withdrawal of consent. Dose reductions to 600 mg, 400 mg and 200 mg BID were permitted due to toxicities.

The primary endpoint was a progression-free survival (PFS) rate (defined as not experiencing progression or death) at 16 weeks for patients with MCL and at 24 weeks for patients with FL, LPL/WM and MZL. Secondary endpoints included evaluation of safety, overall response rate (ORR), duration of response and time to response. An independent review committee (IRC) assessed PFS and other tumour control endpoints. Tumour response was assessed by CT/MRI every 8 weeks during the first 24 weeks on study and then every 12 weeks up to 72 weeks. After 72 weeks, scans were performed at least every 6 months. A bone marrow biopsy and aspirate were required for all subjects who achieved a CR for confirmatory purposes and at the time of disease progression. In LPL/WM patients, in addition to nodal and marrow assessments, serial measurements of serum monoclonal IgM both by SPEP and immunoelectrophoresis were required. Tumour response was assessed per the revised response criteria for malignant lymphoma (Cheson *et al*, 2007). AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4·03 (https://www.eortc.be/services/doc/ctc/CTCAE_4·03_2010-06-14_QuickReference_5x7.pdf).

A Bayesian, continuous data review approach using a Beta-Binomial model was applied to FL and MCL cohorts separately for futility assessment. The review began when the first 10 subjects' primary endpoints (PFS at 24 weeks for FL or PFS at 16 weeks for MCL) became available in each cohort. If the probability of PFS at 24 weeks or 16 weeks being less than 0·2 is greater than 0·9 given the data in a cohort, enrolment can be terminated, taking into account other clinical data and drug exposure. Otherwise, enrolment would continue until a total of 40 subjects were enrolled in each cohort. With the decision rule employed, and assuming that enrolment would be terminated once the futility criterion is met, a sample size of 40 subjects in a cohort gives a high probability (~84%) of claiming futility when the true PFS rate is low (0·1). When the true PFS rate is high (0·5), this design has a low probability (0·15%) of claiming futility.

Subjects with LPL/WM or MZL were enrolled into a non-FL iNHL cohort without a futility analysis. This non-FL iNHL cohort was planned to continue to a maximum total of 45 subjects with LPL/WM, MZL or SLL (the SLL group is not included in this report). No futility analysis was planned because of the rarity of these lymphoma subtypes and the relative dearth of standard of care therapies to set a threshold for a meaningful response rate.

The study protocol, amendments, informed consent according to the Declaration of Helsinki and other information that required pre-approval were approved by the relevant institutional review boards. A more detailed description of the methods has been previously published (Sharman *et al*, 2015).

Table I. Baseline characteristics by cohort.

	FL n = 41	LPL/WM n = 17	MZL n = 17	MCL n = 39	Total N = 114
Male, n (%)	20 (48·8)	11 (64·7)	11 (64·7)	25 (64·1)	67 (58·8)
Median age, years (range)	67 (41–89)	72 (47–89)	65 (52–83)	72 (49–92)	71 (41–92)
Median prior therapies, n (range)	3 (1–14)	3 (1–8)	3 (1–8)	2 (1–6)	3 (1–14)
Anti-CD20 antibody, n (%)	41 (100)	17 (100)	16 (94·1)	37 (94·9)	111 (97·4)
Any alkylating agent, n (%)	39 (95·1)	12 (70·6)	14 (82·4)	37 (94·9)	102 (89·5)
Bendamustine	21 (51·2)	4 (23·5)	10 (58·8)	17 (43·6)	52 (45·6)
Any purine analogue, n (%)	2 (4·9)	4 (23·5)	6 (35·3)	4 (10·3)	16 (14)
Fludarabine	2 (4·9)	3 (17·6)	6 (35·3)	3 (7·7)	14 (12·3)
Anthracyclines, n (%)	21 (51·2)	1 (5·9)	3 (17·6)	30 (76·9)	55 (48·2)

FL, Follicular lymphoma; LPL/WM, Lymphoplasmacytoid lymphoma/Waldenström macroglobulinaemia; MCL, Mantle cell lymphoma; MZL, Marginal zone lymphoma.

Results

Patient characteristics and disposition

There were 41, 17, 17 and 39 patients included in the FL, LPL/WM, MZL and MCL cohorts respectively. Baseline characteristics and disposition are listed by cohort in Table I. The median number of prior treatment regimens was 3 (range 1–14) across cohorts. Prior treatments included anti-CD20 antibodies, alkylating agents, bendamustine and anthracyclines. The most common reasons for discontinuation of study drug across cohorts were progressive disease and treatment-emergent adverse events (TEAEs). As of 3 April 2017, >95% of patients in all cohorts had discontinued treatment with entospletinib. The median duration on treatment was 16·6 weeks (range 0·7–182·6 weeks) across cohorts.

Table II. Summary of adverse events (AEs) and deaths across all cohorts.

Patient, n (%)	Total (N = 114)
AE	
Any	113 (99·1)
Grade ≥3	84 (73·7)
Grade ≥3 related to entospletinib	49 (43·0)
Serious	37 (32·5)
Serious related to entospletinib	6 (5·3)
AE leading to	
Study drug dose reduction	9 (7·9)
Study drug interruption	61 (53·5)
Study drug discontinuation	17 (14·9)
Death	
Within 30 days of last dose	9 (7·9)
Cause of death	
Progressive disease	5 (4·4)
Other	4 (3·5)

Safety

Almost all patients (99%) across disease cohorts experienced a TEAE, with grade ≥3 TEAEs ranging from 65% to 82%. Serious adverse events (SAEs) occurred at rates ranging from 22% to 41%, TEAEs leading to interruption of entospletinib occurred at rates ranging from 49% to 65%, and TEAEs leading to discontinuation of entospletinib occurred at rates of 8% to 29% across cohorts. TEAEs leading to death within 30 days of the last dose occurred in 1 patient (6%) in the LPL/WM cohort and 4 patients (13%) in the MCL cohort (Table II).

Rates of TEAEs in each cohort are listed in Tables II–IV. The most common TEAEs regardless of causality occurring in ≥20% of patients across cohorts were fatigue, nausea, diarrhoea, vomiting, constipation, pyrexia and decreased appetite. Common laboratory abnormalities were anaemia, neutropenia, thrombocytopenia, increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin.

There were 3 (7%), 1 (6%) and 5 (13%) deaths within 30 days of the last dose in the FL, LPL/WM and MCL cohorts respectively. The deaths in the FL cohort were attributed to progressive disease. In the LPL/WM cohort, the death was attributed to progressive disease and a TEAE (acute respiratory distress). In the MCL cohort, 1 patient died of progressive disease and 4 patients died due to other causes [cardiac arrest (n = 1), febrile neutropenia (n = 1), gastrointestinal haemorrhage (n = 1) and intestinal obstruction (n = 1)] judged by the investigator not to be related to study drug (Table II).

Efficacy

In patients with FL, LPL/WM or MZL, the rates of PFS at 24 weeks were 51·5% (95% CI: 32·8–67·4%), 69·8% (95% CI 31·8–89·4%) and 46·2% (95% CI 18·5–70·2%), respectively (Fig 1A–C). PFS at 16 weeks in the MCL cohort was 63·9% (45–77·8%) and 56·6% (95% CI 37·5–71·8%) at 24 weeks (Fig 1 D). Median PFS was 5·7 months (95% CI: 3·6–11·2 months), 10·9 months (95% CI 2·1–13·7), 5·5 months

Table III. TEAEs, SAEs, and laboratory abnormalities across all cohorts.

TEAE of any grade ≥15%, *n* (%)	Total (*N* = 114)
Fatigue	65 (57·0)
Nausea	55 (48·2)
Diarrhoea	52 (45·6)
Constipation	30 (26·3)
Decreased appetite	28 (24·6)
Cough	27 (23·7)
Pyrexia	27 (23·7)
Vomiting	25 (21·9)
Anaemia	21 (18·4)
Headache	21 (18·4)
Dizziness	20 (17·5)
Dyspepsia	20 (17·5)
ALT increased	19 (16·7)
Dyspnoea	18 (15·8)
Upper respiratory tract infection	18 (15·8)
SAE of any grade ≥2%	
Dyspnoea	5 (4·4)
Acute kidney injury	4 (3·5)
Anaemia	3 (2·6)
Febrile neutropenia	3 (2·6)
Pneumonia	3 (2·6)
Laboratory abnormalities of any grade ≥20%: serum chemistry	
Creatinine increased	66 (57·9)
ALT increased	50 (43·9)
AST increased	41 (36·0)
Hyperglycaemia	37 (32·5)
Alkaline phosphatase increased	34 (29·8)
Hypoalbuminaemia	30 (26·3)
Total bilirubin increased	30 (26·3)
Hyponatraemia	28 (24·6)
Indirect blood bilirubin increased	23 (20·2)
Laboratory abnormalities of any grade ≥20%: haematology	
Anaemia	42 (36·8)
Neutropenia	35 (30·7)
Lymphocytes decreased	34 (29·8)
Leucocytes decreased	33 (28·9)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

(95% CI 3·5–22·1) and 5·6 months (95% CI 3·6–8·9) in the FL, LPL/WM, MZL and MCL cohorts respectively.

ORRs were 17·1% (95% CI 8·3–29·7%), 35·3% (95% CI 16·6–58·0%), 11·8% (95% CI 2·1–32·6%) and 17·9% (95% CI 8·7–31·1%) in the FL, LPL/WM, MZL and MCL cohorts, respectively. All responders achieved partial responses or minor responses (for LPL/WM). No patient achieved a CR. Stable disease was achieved in 21 (51%), 5 (29%), 12 (71%) and 22 (56%) patients with FL, LPL/WM, MZL and MCL, respectively (Table V). Eleven (27%), 1 (6%), 2 (12%) and 7 (18%) patients with FL, LPL/WM, MZL and MCL, respectively, had progressive disease. No assessments were conducted in 2 cases (5%) of FL, 5 cases (29%) of LPL/WM, 1 case (6%) of MZL and 3 cases (8%) of MCL.

Nodal response (≥50% decrease in the sum of the products in the index nodal lesions from baseline) as assessed by the IRC is illustrated in Fig 2. The median duration of response to entospletinib treatment was 7·6 months in FL, 9 months in LPL/WM and 7·5 months in MCL. Median duration of response was not reached in patients with MZL.

Table IV. Grade ≥3 TEAEs, SAEs, and laboratory abnormalities across all cohorts.

TEAE grade ≥3 (≥5%), *n* (%)	Total (*N* = 114)
ALT increased	18 (15·8)
Anaemia	13 (11·4)
Fatigue	12 (10·5)
AST increased	10 (8·8)
Neutropenia	10 (8·8)
Dyspnoea	9 (7·9)
SAE grade ≥3 (≥2%), *n* (%)	
Dyspnoea	5 (4·4)
Acute kidney injury	4 (3·5)
Anaemia	3 (2·6)
Febrile neutropenia	3 (2·6)
Pneumonia	3 (2·6)
Laboratory abnormalities ≥grade 3 (≥5%): serum chemistry	
ALT increased	21 (18·4)
AST increased	15 (13·2)
Hyperglycaemia	13 (11·4)
Hyponatraemia	10 (8·8)
Laboratory abnormalities ≥grade 3 (≥5%): haematology	
Lymphocyte count decreased	16 (14·0)
Anaemia	12 (10·5)
Neutropenia	10 (8·8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Discussion

Recently, there has been a significant expansion of new therapies for B-cell malignancies that target the BCR pathway. Constitutive BCR signalling is a critical survival pathway for malignant B cells, and interruption of this pathway by inhibition of its various components has emerged as a productive strategy in the treatment of these disorders. The approval of agents that target BTK (ibrutinib, acalabrutinib) and PI3K (idelalisib, copanlisib) has improved the range of therapeutic options and the natural history of these disorders.

Syk is positioned upstream from BTK and PI3K in the BCR signalling pathway and is a target for inhibition. Indeed, the first report of successful therapeutic targeting of BCR signalling in B-cell malignancies was with the Syk inhibitor fostamatinib (Friedberg *et al*, 2010). Although activity of this particular agent was limited, it demonstrated the feasibility of this approach and ushered in the age of targeted therapy for B-cell malignancies.

In this report, we describe the efficacy and safety of the Syk inhibitor entospletinib as monotherapy in patients with

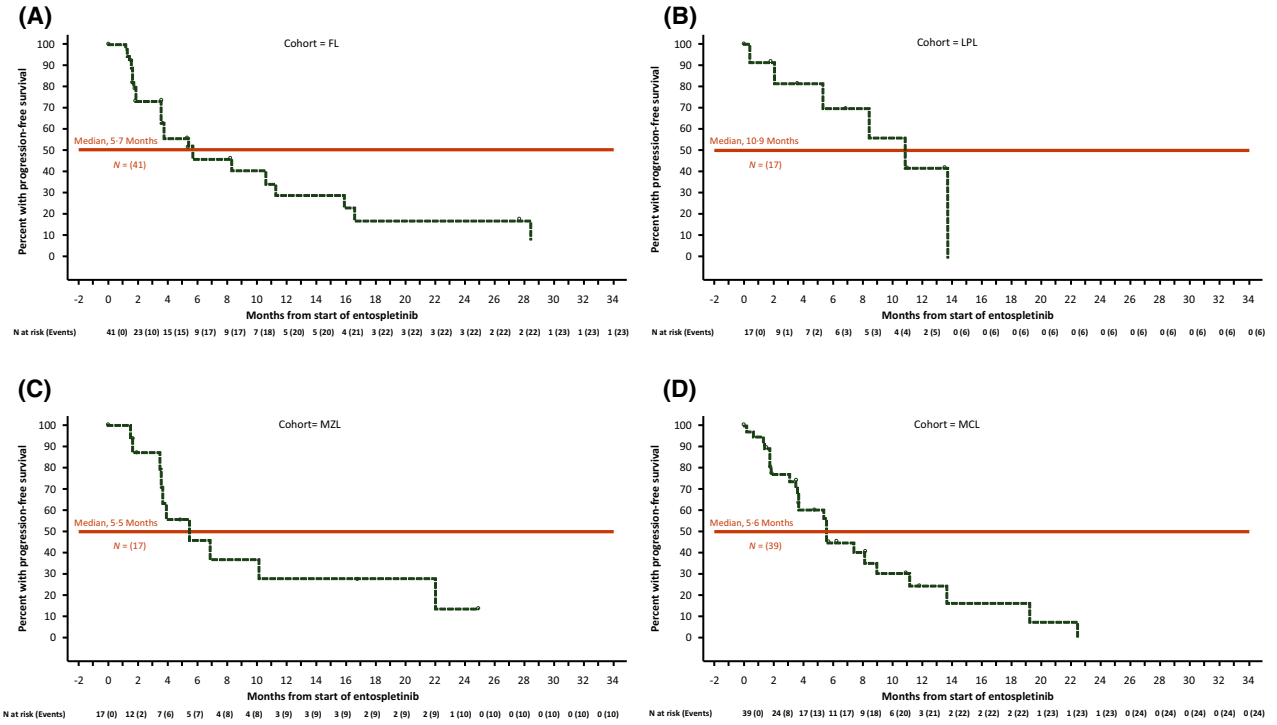

Fig 1. Independent review committee-assessed progression-free survival (PFS). (A) Follicular lymphoma (FL, $n = 41$). PFS rate at 24 weeks: 51·5% [95% confidence interval (CI) 32·8–67·4]; Median follow-up: 3·6 months (1·6–5·6); Median PFS: 5·7 months (95% CI 3·6–11·2). (B) Lymphoplasmacytoid lymphoma/Waldenström macroglobulinaemia (LPL/WM; $n = 17$). PFS rate at 24 weeks: 69·8% (95% CI 31·8–89·4); Median follow-up: 2·1 months (0–8·5); Median PFS: 10·9 months (95% CI 2·1–13·7). (C) Marginal zone lymphoma (MZL; $n = 17$). PFS rate at 24 weeks: 46·2% (95% CI 18·5–70·2); Median follow-up: 3·6 months (1·9–6·9); Median PFS: 5·5 months (95% CI 3·5–22·1). (D) Mantle cell lymphoma (MCL; $n = 39$). Median PFS: 5·6 months (95% CI 3·6–8·9; Median follow-up: 3·7 months (1·7–7·4).

Table V. Independent review committee-assessed best overall responses.

	FL $n = 41$	LPL/WM $n = 17$	MZL $n = 17$	MCL $n = 39$
Best overall response, *n* (%)				
Complete response	0	0	0	0
Partial response	7 (17)	2 (11·8)	2 (11·8)	7 (17·9)
Minor response	0	4 (23·5)	0	0
Stable disease	21 (51·2)	5 (29·4)	12 (70·6)	22 (56·4)
Progressive disease	11 (26·8)	1 (5·9)	2 (11·8)	7 (17·9)
Assessment not done	2 (4·9)	5 (29·4)	1 (5·9)	3 (7·7)
Overall response rate, n (%)	7 (17·1)	6 (35·3)	2 (11·8)	7 (17·9)
90% CI, %	8·3-29·7	16·6-58·0	2·1-32·6	8·7-31·1

CI, confidence interval; FL, follicular lymphoma; LPL, lymphoplasmacytoid lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

haematological malignancies. Activity as a single agent was modest, with ORRs of 17·1% in FL, 35·3% in LPL/WM, 11·8% in MZL and 17·9% in MCL. The most common toxicities reported for entospletinib were fatigue, nausea and diarrhoea (any grade). Grade 3–4 neutropenia was seen in approximately 9% of subjects; grade 3–4 AST and ALT elevation without any clinically significant increase of bilirubin was seen in approximately 15% of patients. Grade ≥3 TEAEs ranged from 65% to 82% across the cohorts. Entospletinib was dose reduced in 28% of patients and discontinued due to toxicity in 15% of patients.

The relatively low response rate as a single agent suggests that entospletinib should be investigated in combination with other agents. *In vitro* and *in vivo* studies show synergistic activity with vincristine in a broad panel of NHL cell lines (Axelrod *et al*, 2015) and a model of acute lymphoblastic leukaemia (Loftus *et al*, 2017). Syk inhibition may also reduce resistance to venetoclax, a BCL2 inhibitor,

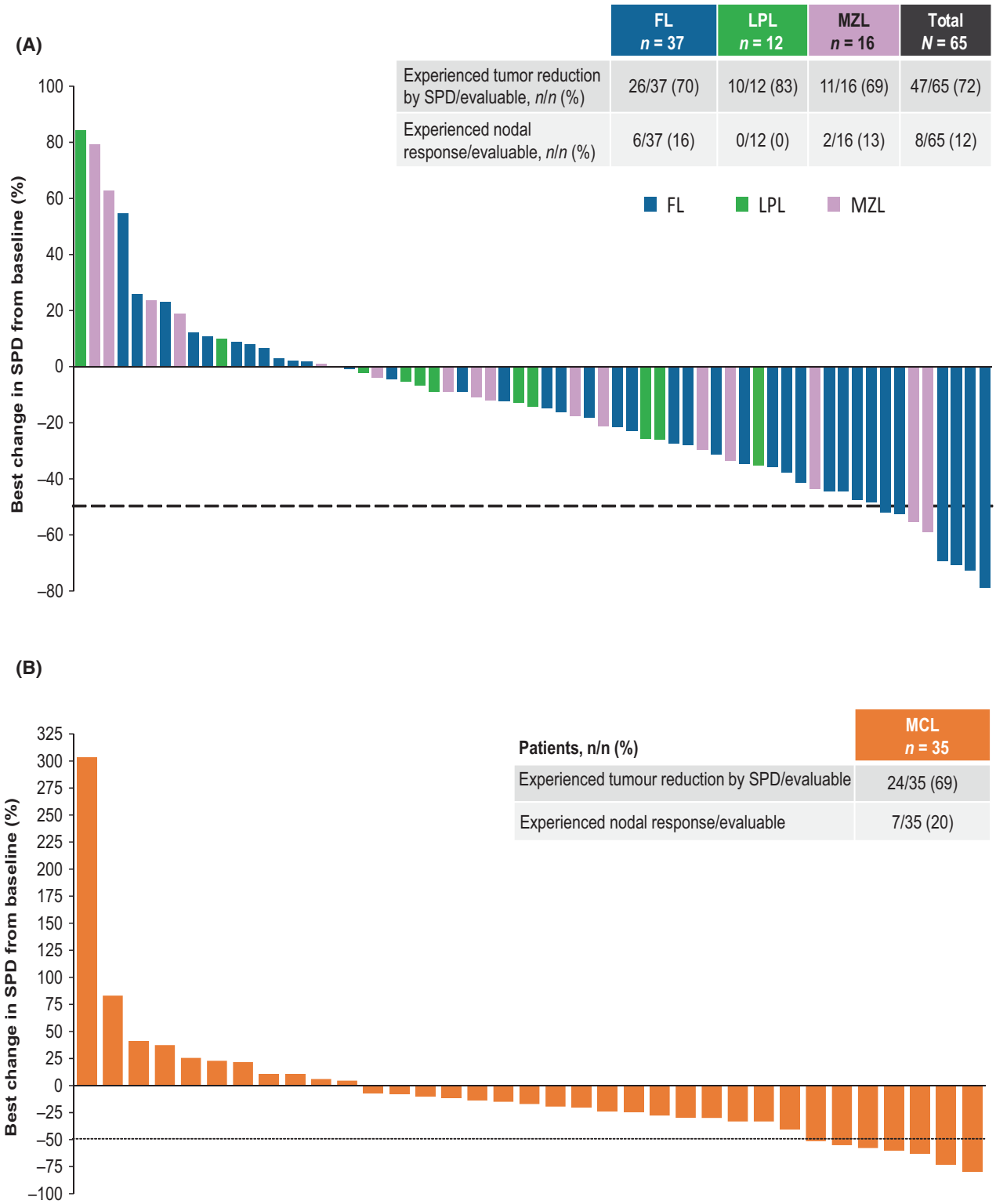

Fig 2. Nodal responses (≥50% decrease from baseline in sum of product diameters) in the cohorts of patients with (A) indolent non-Hodgkin lymphoma and (B) MCL. FL, follicular lymphoma; LPL, lymphoplasmacytoid lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SPD, sum of product diameters.

through downregulation of Mcl1 (Bojarczuk *et al*, 2016). Clinical trials are underway studying combinations of entospletinib with vincristine and with obinutuzumab in a variety of B-cell malignancies.

A number of other Syk inhibitors are also in clinical development. These include cerdulitinib, a dual Syk/JAK inhibitor, and TAK-659, a dual Syk/FLT3 inhibitor. In small phase I studies, both of these molecules showed promising results in iNHL. Cerdulitinib resulted in partial responses in 3 of 6 (50%) of subjects with FL (Hamlin *et al*, 2017); TAK-659 induced a partial response in 3 of 3 FL subjects (Kaplan *et al*, 2016). These results, although quite preliminary, lend support to the hypothesis that Syk inhibition may be most successful when other relevant signalling pathways are inhibited simultaneously.

In conclusion, entospletinib demonstrated modest single agent activity in iNHL and had a toxicity profile that was manageable and comparable to other BCR pathway small-molecule inhibitors, such as idelalisib and ibrutinib. Further study of entospletinib in rational combinations with other therapeutic agents is warranted.

Acknowledgements

The authors would like to thank Esteban Abella-Dominicis for his scientific contributions to the study during his tenure at Gilead Sciences, Inc., and Dr. Arati V. Rao for manuscript review and writing. Editorial assistance was provided by Impact Communication Partners, Inc. This clinical study was supported by research funding from Gilead Sciences, Inc. (Foster City, CA, USA).

Authorship contributions

J.P.S. designed the research study; V.J. contributed essential reagents or tools; D.J.A., M.S., K.S.K., V.J., S.A., L.M.K., W.S., D.P.D., C.A.Y. and J.P.S. performed research; D.J.A., M.S., A.F.T., K.S.K., S.A., W.S., W.Y. and J.P.S. analysed data; D.J.A., M.S. and A.F.T. interpreted data; All authors participated in drafting and/or critically revising the manuscript, and its final approval.

Conflict-of-interest disclosures

D.J.A., A.F.T., V.J., and L.M.K. declared no conflicts of interest. K.S.K. has been a consultant and received research funding from Gilead Science Inc.; received honoraria from TG Therapeutics. 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., Novartis AG; and served on the Board of Directors/advisory committee for Knight Therapeutics Inc.. D.P.D. has consulted and served on the Board of Directors/advisory committee for Juno Therapeutics. M.S. has received remunerations from AstraZeneca, Seattle Genetics, Merck, and Kite. W.Y. is a current or former employee of, and has owned stock/held ownership interests in Gilead Sciences, Inc. W.S. is a current employee of, has conducted research for, and has owned stock/held ownership interests in Gilead Sciences, Inc. C.A.Y. has received research funding from Gilead Sciences, Inc; has received research funding and been a consultant for Seattle Genetics and Bristol-Myers Squib. J.P.S. a current or former employee of US Oncology, Inc.; has consulted and conducted research for Gilead Sciences, Inc., Genentech, Inc., Pharmacyclics LLC, AbbVie Inc., TG Therapeutics, Inc., and Seattle Genetics.

Key Points

- Entospletinib monotherapy had limited activity and acceptable tolerability in patients with relapsed or refractory iNHL and MCL
- Entospletinib is currently being evaluated in iNHL and MCL in combination with chemotherapy and BCR-targeted agents

References

Anastasia, A. & Rossi, G. (2016) Novel drugs in follicular lymphoma. *Mediterranean Journal of Hematology and Infectious Diseases*, **8**, e2016061.

Axelrod, M.J., Fowles, P., Silverman, J., Clarke, A., Tang, J., Rousseau, E., Webb, H. & Di Paolo, J. (2015) The combination of entospletinib and vincristine demonstrates synergistic activity in a broad panel of hematological cancer cell lines and anti-tumor efficacy in a DLBCL xenograft model. *Blood*, **126**, 5123.

Bojarczuk, K., Sasi, B.K., Gobessi, S., Innocenti, I., Possato, G., Laurenti, L. & Efremov, D.G. (2016) BCR signaling inhibitors differ in their ability to overcome Mcl-1-mediated resistance of CLL B cells to ABT-199. *Blood*, **127**, 3192–3201.

Buchner, M., Baer, C., Prinz, G., Dierks, C., Burger, M., Zenz, T., Stilgenbauer, S., Jumaa, H., Veelken, H. & Zirlik, K. (2010) Spleen tyrosine kinase inhibition prevents chemokine- and integrin-mediated stromal protective effects in chronic lymphocytic leukemia. *Blood*, **115**, 4497–4506.

Casulo, C., Byrtek, M., Dawson, K.L., Zhou, X., Farber, C.M., Flowers, C.R., Hainsworth, J.D., Maurer, M.J., Cerhan, J.R., Link, B.K., Zelenetz, A.D. & Friedberg, J.W. (2015) Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **33**, 2516–2522.

Cheson, B.D., Pfistner, B., Juweid, M.E., Gascoyne, R.D., Specht, L., Horning, S.J., Coiffier, B., Fisher, R.I., Hagenbeek, A., Zucca, E., Rosen, S.T., Stroobants, S., Lister, T.A., Hoppe, R.T., Dreyling, M., Tobinai, K., Vose, J.M., Connors, J.M., Federico, M. & Diehl, V.; International Harmonization Project on Lymphoma. (2007) Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, **25**, 579–586.

Chiorazzi, N. & Ferrarini, M. (2003) B cell chronic lymphocytic leukemia: lessons learned from studies of the B cell antigen receptor. *Annual Review of Immunology*, **21**, 841–894.

Currie, K.S., Kropf, J.E., Lee, T., Blomgren, P., Xu, J., Zhao, Z., Gallion, S., Whitney, J.A., Maclin, D., Lansdon, E.B., Maciejewski, P., Rossi, A.M., Rong, H., Macaluso, J., Barbosa, J., Di Paolo, J.A. & Mitchell, S.A. (2014) Discovery of GS-9973, a selective and orally efficacious inhibitor of spleen tyrosine kinase. *Journal of Medicinal Chemistry*, **57**, 3856–3873.

Fakhri, B. & Kahl, B. (2017) Current and emerging treatment options for mantle cell lymphoma. *Therapeutic Advances in Hematology*, **8**, 223–234.

Fowler, N. & Davis, E. (2013) Targeting B-cell receptor signaling: changing the paradigm. *Hematology/The Education Program of the American Society of Hematology*, **2013**, 553–560.

Friedberg, J.W., Sharman, J., Sweetenham, J., Johnston, P.B., Vose, J.M., Lacasce, A., Schaefer-Cutillo, J., De Vos, S., Sinha, R., Leonard, J.P., Cripe, L.D., Gregory, S.A., Sterba, M.P., Lowe, A.M., Levy, R. & Shipp, M.A. (2010) Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood*, **115**, 2578–2585.

Gobessi, S., Laurenti, L., Longo, P.G., Carsetti, L., Berno, V., Sica, S., Leone, G. & Efremov, D.G. (2009) Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. *Leukemia*, **23**, 686–697.

Hamlin, P., Farber, C., Fenske, T., Khatcheressian, J., Miller, C., Munoz, J., Patel, M., Smith, S., Stevens, D., Pandey, A., Birrell, M., Leeds, J., Wang, Y.L., Coffey, G. & Curnutte, J. (2017) The Dual SYK/JAK inhibitor cerdulatinib demonstrates complete inhibition of SYK and JAK and rapid tumor responses in a phase 2 study in patients with relapsed/refractory B Cell malignancies. *Haematologica*, **102**, S773.

Kaplan, J.B., Gordon, L.I., Infante, J.R., Popat, R., Rambaldi, A., Madan, S., Patel, M.R., Gritti, G., Ng, C-H., Chau, I., Radford, J.A., de Oteyza, J.P., Zinzani, P.L., Faucette, S., Sheldon-Waniga, E., Williams, M., Stumpo, K., Shou, Y., Carpio, C. & Bosch, F. (2016) Updated results from a phase 1 study of TAK-659, an investigational and reversible SYK inhibitor, in patients (Pts) with advanced solid tumor or lymphoma malignancies. *Blood*, **128**, 624.

Kipps, T.J. (2007) The B-cell receptor and ZAP-70 in chronic lymphocytic leukemia. *Best Practice and Research. Clinical Haematology*, **20**, 415–424.

Loftus, J.P., Yahiaoui, A., Shen, F., Lopez, D., Mikaelian, I., Brown, P.A., Tannheimer, S., Forslund, A. & Tasian Sarah, K. (2017) Enhanced efficacy of the Syk inhibitor entospletinib and chemotherapy in infant acute lymphoblastic leukemia. *Blood*, **130**, 2611.

Quiroga, M.P., Balakrishnan, K., Kurtova, A.V., Sivina, M., Keating, M.J., Wierda, W.G., Gandhi, V. & Burger, J.A. (2009) B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. *Blood*, **114**, 1029–1037.

Ramanathan, S., Di Paolo, J.A., Doan, T. & Burge, D. (2013) Single and multiple dose-ranging evaluation of safety, pharmacokinetics, and pharmacodynamics of GS-9973, a novel pSYK inhibitor. *Cancer Research*, **73**(Supplement), Abstract–32.

Sharman, J. & Di Paolo, J. (2016) Targeting B-cell receptor signaling kinases in chronic lymphocytic leukemia: the promise of entospletinib. *Therapeutic Advances in Hematology*, **7**, 157–170.

Sharman, J., Hawkins, M., Kolibaba, K., Boxer, M., Klein, L., Wu, M., Hu, J., Abella, S. & Yasenchak, C. (2015) An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. *Blood*, **125**, 2336–2343.

Spurgeon, S.E., Till, B.G., Martin, P., Goy, A.H., Dreyling, M.P., Gopal, A.K., LeBlanc, M., Leonard, J.P., Friedberg, J.W., Baizer, L., Little, R.F., Kahl, B.S. & Smith, M.R. (2017) Recommendations for clinical trial development in mantle cell lymphoma. *Journal of the National Cancer Institute*, **109**, 1–10.

Stevenson, F.K. & Caligaris-Cappio, F. (2004) Chronic lymphocytic leukemia: revelations from the B-cell receptor. *Blood*, **103**, 4389–4395.

Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edn. International Agency for Research on Cancer Press, Lyon, France.

Treon, S.P., Tripsas, C.K., Meid, K., Warren, D., Varma, G., Green, R., Argyropoulos, K.V., Yang, G., Cao, Y., Xu, L., Patterson, C.J., Rodig, S., Zehnder, J.L., Aster, J.C., Harris, N.L., Kanan, S., Ghobrial, I., Castillo, J.J., Laubach, J.P., Hunter, Z.R., Salman, Z., Li, J., Cheng, M., Clow, F., Graef, T., Palomba, M.L. & Advani, R.H. (2015) Ibrutinib in previously treated Waldenström's macroglobulinemia. *New England Journal of Medicine*, **372**, 1430–1440.

Williams, M.E., Dreyling, M., Winter, J., Muneer, S. & Leonard, J.P. (2010) Management of mantle cell lymphoma: key challenges and next steps. *Clinical Lymphoma, Myeloma and Leukemia.*, **10**, 336–346.

