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

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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; Gobetti et al, 2009). Expression of Syk occurs predominately 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, 2010).
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 assay 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 (Swerdlov 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 \( \geq 1 \) lesion that measures \( \geq 2.0 \) cm in the longest diameter and \( \geq 1.0 \) 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).
Marginal zone lymphoma.

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.

#### 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 1D). 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 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.

### 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)        |

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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)      |
| Dyspnoea                      | 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 (43.5)      |
| AST increased                 | 41 (36.0)      |
| Hyperglycaemia                | 37 (32.5)      |
| Alkaline phosphatase increased| 34 (29.8)      |
| Hypalbuminaemia               | 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 (31%), 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.

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 fosfomatinib (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
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,

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**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)   | 0          |
| 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.
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 cerdulatinib, 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. Cerdulatinib 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.

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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 supported by research funding from Gilead Sciences, Inc.; has consulted and conducted research for Gilead Sciences, Inc; has received research funding and been on the Board of Directors/advisory committee for Knight 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., and Kite. W.Y. is a current or former employee of, 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. 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 and Bristol-Myers Squib.

Conflicts-of-interest disclosures

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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

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