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Ibrutinib for the treatment of Bing-Neel syndrome: A multicenter study

Short title

Ibrutinib for Bing-Neel syndrome

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Key Points

- Ibrutinib was administered to 28 patients with Bing-Neel syndrome (BNS)
- Ibrutinib showed rapid and durable symptomatic and radiological responses in patients with BNS

Abstract

The treatment of patients with Bing-Neel syndrome (BNS) is not standardized. We included patients with Waldenstrom macroglobulinemia (WM) and a radiological and/or cytological diagnosis of BNS treated with ibrutinib monotherapy. Response assessment was based on criteria for BNS from the 8th International Workshop for WM. Survival from from BNS diagnosis (BNS survival), survival from ibrutinib initiation to last follow-up or death (ibrutinib survival) and time from ibrutinib initiation to ibrutinib discontinuation for toxicity, progression or death (event-free survival, EFS) were estimated. Twenty-eight patients were included in our study. The median age at BNS diagnosis was 65 years. Ibrutinib was the first line of treatment for BNS in 39% of patients. Ibrutinib was administered orally at a dose of 560 mg and 420 mg once daily in 46% and 54% of patients, respectively. Symptomatic and radiologic improvements were seen in 85% and 60% of patients within 3 months of therapy. At best response, 85% of patients had improvement or resolution of BNS symptoms, 83% had improvement or resolution of radiological abnormalities, and 47% had cleared the disease in the cerebrospinal fluid. The 2-year EFS rate on ibrutinib was 80% (95% CI 58-91%), the 2-year ibrutinib

survival rate was 81% (95% CI 49-94%) and the 5-year BNS survival rate was 86% (95% CI 63-95%). Ibrutinib therapy is effective in patients with BNS and should be considered as a treatment option in these patients.

Keywords

Bing-Neel syndrome; Waldenstrom macroglobulinemia; ibrutinib; BTK inhibitors

Introduction

Bing-Neel syndrome (BNS) is a rare condition seen in approximately 1% of patients with a diagnosis of Waldenstrom macroglobulinemia (WM) [1]. BNS is a clinicopathological entity caused by WM cells gaining access to the central nervous system (CNS) and causing a variety of neurological deficits in patients affected by this process [2, 3]. Interestingly, Bing and Neel described two cases of neurological deterioration occurring in patients with macroglobulinemia in 1937, seven years before the seminal description of patients with macroglobulinemia, anemia, coagulopathy and incipient myelomatosis by Jan Waldenstrom [4, 5].

The therapy for BNS is not standardized and limited to antineoplastic agents with good CNS penetration [1]. Agents such as high-dose methotrexate, cytarabine and fludarabine, however, are associated with well know toxicities such as myelosuppression, immunosuppression and mucositis [6]. The oral Bruton Tyrosine Kinase (BTK) inhibitor ibrutinib is approved in the United States (US) and Europe for the treatment of patients with symptomatic WM. There have been a few cases reporting clinical efficacy of ibrutinib in patients with BNS [7-10]. In one patient, we demonstrated blood-brain barrier (BBB) penetration by ibrutinib in a dose-dependent manner [9]. However, data on response and survival outcomes to ibrutinib in BNS remain limited.

We therefore carried out a retrospective study on patients who received ibrutinib for a diagnosis of symptomatic BNS. The aims of our study were to report on response rates, survival outcomes and safety of ibrutinib therapy in patients with BNS.

Methods

Patient selection

We identified patients older than 18 years of age with a clinicopathological diagnosis of WM [11], who also had a diagnosis of BNS made at the time of or after the diagnosis of WM [1]. BNS was defined as the presence of malignant lymphoplasmacytic cells in the cerebrospinal fluid (CSF) demonstrated by cytology and/or flow cytometry or brain tissue biopsy, with or without evidence of leptomeningeal enhancement or brain masses using MRI techniques. Finally, patient must have received ibrutinib for the treatment of BNS. The Institutional Review Boards from all participating centers approved the present study.

Data collection

Pertinent clinical data were gathered at the time of WM diagnosis, at the time of BNS diagnosis and at the time of ibrutinib therapy initiation for BNS. Response to ibrutinib therapy was evaluated based on current response criteria for BNS and WM [1, 12]. Briefly, the response criteria for BNS defines complete response as the complete

resolution of symptoms as well as radiological and cytological evidence of BNS, partial response as radiological and/or symptomatic improvement but with clearance of cytological findings, and no response as no improvement in symptoms, radiological or cytological abnormalities. Data on toxicity were gathered retrospectively and reporting was based on Common Terminology Criteria for Adverse Events, version 5.0 [13]. We calculated time from WM diagnosis to BNS diagnosis, time from BNS diagnosis to ibrutinib initiation, time from ibrutinib initiation to unacceptable toxicity, progressive disease or death from any cause (event-free survival or EFS), time from ibrutinib initiation to last follow-up or death from any cause (ibrutinib survival), time from BNS diagnosis to last follow-up or death (BNS survival) from any cause, and time from WM diagnosis to last follow-up or death from any cause (WM survival).

Data sharing statement

For original data, please contact jorgej_castillo@dfci.harvard.edu.

Statistical analysis

Clinical characteristics are presented using descriptive statistics such as medians and ranges, and numbers and proportions. Time to events were estimated using the Kaplan-Meier method for incomplete observations [14]. Comparisons between groups were assessed using the log-rank test [15]. All calculations and graphs were obtained using STATA, version 13.1 (College Station, TX, USA).

Results

Patients' characteristics

Twenty-eight patients were included in this study and were diagnosed with WM between 1992 and 2018. The median age at diagnosis of WM was 60 years (range 38-80 years). Sixteen patients (57%) were men. The patients were diagnosed with BNS between 2011 and 2018. At the time of BNS diagnosis, the median age was 65 years (range 38-81 years). The median time from WM to BNS diagnosis was 48 months (range 0-320 months). Ten patients (36%) were diagnosed with BNS within 12 months of WM diagnosis. Eleven patients (39%) were previously untreated for their WM at the time of BNS diagnosis. Of the 17 patients who were previously treated for their WM, the median number of WM therapies was 3 (range 1-7). All patients had received anti-CD20 monoclonal antibody therapy, 16 (94%) had received alkylating agents, eight (47%) nucleoside analogues, four (24%) proteasome inhibitors, three (18%) immunomodulating agents and two (12%) underwent autologous stem cell transplant.

BNS presenting symptoms included motor deficits in 13 patients (46%), cognitive deficits in 11 (39%), sensory deficits in 11 (39%), headaches in six (21%), ataxia in five (18%), cranial nerve deficits in five (18%) and seizures in five (18%). Brain and spinal MRI were normal in 3 patients (11%). Of the 25 patients (89%) with MRI findings, 20 (80%) showed leptomeningeal enhancement, three (12%) had intraparenchymal

masses and two had intraparenchymal masses with concurrent leptomeningeal enhancement (8%). CSF cytology were positive for lymphoplasmacytic cells in 27 patients (96%). The diagnosis of BNS was made on a brain biopsy in one patient. CSF flow cytometry revealed clonal B-cells with positive expression of CD19 and/or CD20 and negative expression of CD5 and/or CD10 in 21 patients (75%). The MYD88 L265 mutation was detected in 23 of 24 patients (96%) investigated; 17 of 18 (94%) in bone marrow or other tissues, and 11 of 11 (100%) in CSF. The patient in whom the MYD88 L265P mutation was not detected n the bone marrow had minimal bone marrow involvement by WM, and this could have been a false negative result. In summary, 24 patients had positive findings on MRI, CSF cytology and CSF flow cytometry and/or molecular testing, and four patients had positive findings on MRI and CSF cytology.

The patients were started on ibrutinib therapy between 2014 and 2018. Eleven patients (39%) had not previously received therapy for their BNS. Of the 17 patients who were previously treated for their BNS, the median number of therapies prior to ibrutinib was 1 (range 1-5). The median time from last BNS therapy to ibrutinib was 5 months (range 1-81 months). Nine patients (53%) had received intrathecal chemotherapy, 8 (48%) had received high-dose methotrexate, three (18%) had received bendamustine and three (18%) had received radiotherapy. At the time of ibrutinib initiation, the median serum IgM level was 1,148 mg/dl (range 110-9,360 mg/dl) and median hemoglobin level was 11.8 g/dl (range 7.7-15.2 g/dl). Thirteen patients (46%) received ibrutinib at a dose of 560 mg PO QD and 15 (54%) received ibrutinib at a dose of 420 mg PO QD. Patient-level characteristics at the time of ibrutinib initiation are shown in **Table 1**.

Response outcomes to ibrutinib

At best response, the median serum IgM level decreased to 373 mg/dl (range 54-5,010 mg/dl) and the median hemoglobin level increased to 14.2 g/dl (range 8.8-16 g/dl). Based on WM response criteria, one patient (4%) was in very good partial response, 12 (46%) in partial response, eight (31%) in minor response and five (19%) in stable disease. Data on IgM levels were not available in two patients. Data on BNS symptoms were available in 28 patients, five patients (18%) had resolution, 19 (68%) had improvement and four (14%) had no changes. Data on MRI results were available in 18 patients, two patients (11%) had resolution, 13 (72%) had improvement and three (17%) had no changes. Data on cytological findings were available in 17 patients, eight patients (47%) cleared and nine patients (53%) had persistence of disease. Based on current response criteria, one patient (6%) obtained a complete response (CR), six (35%) obtained a partial response (PR) and ten (59%) had no response. Of the ten patients who did not respond, however, seven had clinical benefit, as five had improvement and two had resolution of symptoms. A summary of symptomatic, radiological and cytological responses at 3, 6 and 12 months and at best response to ibrutinib therapy are shown in **Table 2**.

There were no detectable statistical differences in the rates of symptomatic (p=0.42), radiological (p=0.13) or CSF cytological response (p=0.82) in BNS patients treated with ibrutinib dose of 420 mg versus 560 mg. Also, there was no detectable difference based

on current response criteria (p=0.37). Also, there were no differences in symptomatic (p=0.60), radiological (p=0.49) or CSF cytological response (p=0.40) as well as response based on IWWM criteria (p=0.30) in BNS patients who were previously untreated versus previously treated for BNS.

Survival outcomes to ibrutinib

The median follow-up time from WM diagnosis was 8.7 years (95% CI 4.1-11.5 years), the median follow-up time from BNS diagnosis was 1.9 years (95% CI 1.2-2.3 years) and the median follow-up time from ibrutinib initiation was 1 year (95% CI 0.6-1.7 years). At the time of this report, five patients had stopped taking ibrutinib due to progression or toxicity and three patients have died. The estimated 2-year EFS rate from ibrutinib initiation was 80% (95% CI 58-91%; **Figure 1A**). The estimated 2-year survival rate from ibrutinib initiation was 81% (95% CI 49-94%; **Figure 1B**). The estimated 5-year survival rate from BNS diagnosis was 86% (95% CI 63-95%; **Figure 1C**). There were no detectable differences between patients who were previously treated or untreated for their BNS, or between patients who received ibrutinib dose at 560 mg or 420 mg, with regard to EFS (log-rank p=0.97 and p=0.88, respectively); survival from ibrutinib initiation (log-rank p=0.71 and p=0.82, respectively); or survival from BNS diagnosis (log-rank p=0.95 and p=0.70, respectively). Of the five BNS patients who progressed on ibrutinib, treatments after ibrutinib discontinuation included high-dose methotrexate (n=2), bendamustine and rituximab (n=1), fludarabine and rituximab (n=1), and methotrexate and temozolomide (n=1).

Safety

Thirteen patients (45%) had a reported adverse event. Grade 4 adverse events included neutropenia (n=1). Grade 3 adverse events included pneumonia (n=2), muscle cramps (n=1), bleeding (n=1), atrial fibrillation (n=1) and ventricular tachycardia (n=1). Grade 1 or 2 adverse events included diarrhea (n=3), fatigue (n=2), muscle cramps (n=1), headache (n=1), nausea (n=1), mouth sores (n=1), rash (n=1), bruising (n=1) and neutropenia (n=1). Adverse events leading to ibrutinib discontinuation included muscle cramps (n=1) and ventricular tachycardia (n=1). The causes of death were disease progression (n=1), infection (n=1) and multiple comorbidities (n=1).

Discussion

Ibrutinib is an oral BTK inhibitor, approved by the US Food & Drug Administration and the European Medicines Agency, for the treatment of patients with symptomatic WM. The approval was based on the results of a multicenter, single-arm prospective phase II study in which ibrutinib at a dose of 420 mg by mouth once daily induced an overall response rate of 91%, a major response rate of 73% and a 24-month progression-free survival rate of 69% in 63 previously treated patients [16]. Two additional studies in WM patients, one in 31 rituximab-refractory and one in 30 previously untreated patients, showed similar results [17, 18]. However, patients with BNS were excluded from these studies.

Herein, we present clinical characteristics as well as response and survival outcomes and safety on 28 WM patients with a diagnosis of BNS treated with ibrutinib. Symptomatic and radiological improvements were seen in 84% and 57% of patients within 3 months of ibrutinib therapy. At best response, ibrutinib induced improvement or resolution of BNS-associated symptoms and improvement or resolution of MRI abnormalities in 85% and 82% of patients, respectively. The estimated 2-year probability of BNS patients continuing ibrutinib without toxicity, progression or death was 80%. The toxicity to ibrutinib in this study was consistent with prior studies. Previous studies have reported a 3-year survival rates from BNS diagnosis between 60-70%, and a median time to progression or death to first line treatment of BNS at two years [2, 3]. We believe the outcomes reported here are encouraging and strongly suggest a benefit for the use of ibrutinib in patients with BNS.

Observational data have supported clinical efficacy of ibrutinib in patients with mantle cell lymphoma and chronic lymphocytic leukemia involving the CNS [19, 20]. A few case reports have also suggested clinical efficacy of ibrutinib specifically in WM and BNS [7-10]. In a single case study, plasma and CSF were obtained synchronously from a patient with WM and BNS on ibrutinib 560 mg by mouth once daily, and showed that the ibrutinib levels on this patient's CSF were above 50% the inhibitory concentration for BTK inhibition [9]. A preclinical murine model showed that ibrutinib rapidly crosses the BBB with a median time of 0.3 hours [21]. Additionally, intracerebral entry of ibrutinib

directly correlated with ibrutinib plasma concentrations and ibrutinib dose. Of interest, the CNS distribution of ibrutinib was not different in ventricular and cortical areas.

The optimal dose of ibrutinib in BNS has not yet been defined. Recently, a phase I study in patients with relapsed and/or refractory CNS lymphoma patients showed high efficacy of ibrutinib in this setting [22]. In this study, mean CSF ibrutinib concentrations at 2 hours post ibrutinib dose were higher in patients who received ibrutinib at 840 mg than in patients who received 560 mg (2 ng/ml and 0.8 ng/ml, respectively). Mean CSF ibrutinib concentrations after 1 month of therapy also appeared higher in patients on 840 mg than in patients on 560 mg (3.2 ng/ml and 1.7 ng/ml, respectively). One could hypothesize that higher doses of ibrutinib would translate into deeper and more durable responses in BNS patients. In our study, however, with a median follow-up time on ibrutinib of one year, there did not seem to be a difference in response rates and duration of response between patients who received ibrutinib at doses of 420 mg and 560 mg by mouth once daily. Therefore, 420 mg by mouth once daily is a reasonable starting dose for patients with BNS, and if a desired response were not seen, then increasing ibrutinib to 560 mg by mouth once daily could be advisable.

As per current BNS response criteria, partial response is defined by persistence of symptoms and/or radiological abnormalities but there should be CSF cytological clearance. Therefore, patients with persistence CSF cytological findings would be considered non-responders, despite the clinical benefit obtained with therapy. An important point of controversy is the persistence of malignant cells observed in the CSF

of BNS patients who otherwise had symptomatic and/or radiological improvement to ibrutinib therapy. A similar phenomenon was observed in studies evaluating ibrutinib in patients with symptomatic WM, in which there was bone marrow persistence of disease despite marked improvements in symptoms, hematologic parameters and serum IgM levels [16-18]. A modulating rather than cytotoxic effect of ibrutinib could, at least in part, explain this phenomenon. However, in a previous study, approximately half of BNS patients treated with standard therapies had CSF cytological persistence of disease [2]. This finding would suggest revising the current response criteria to permit persistence of CSF cytological findings in the partial response category.

Limitations of our study include the small sample size and its retrospective nature. BNS is a rare condition, and our sample size of 28 patients treated with ibrutinib could be considered large. As an example, two (relatively) large case series on BNS included 35 and 44 patients [2, 3]. Also, several practice-changing prospective studies in WM have had similar sample sizes [17, 18, 23-26]. Our study could have been affected by case selection bias and may overestimate ibrutinib efficacy. However, our cohort included BNS patients from several centers and with clinical features consistent with prior studies. For example, in our study, the median age at BNS diagnosis was 60 years, which is similar to previous reports [2, 3]. Therefore, our sample could be considered representative of the population under study. Also, given the rarity of BNS, a prospective study evaluating ibrutinib specifically in BNS will unlikely be done. Therefore, a retrospective study can provide observations of important clinical value.

Conclusion

Our results show that ibrutinib monotherapy, administered at a dose of 420 mg or 560 mg by mouth once daily, can induce durable responses with acceptable toxicity in patients with BNS. Ibrutinib, therefore, should be considered a treatment option for these patients in the frontline and relapsed settings. Longer follow-up is needed to better define the optimal dose of ibrutinib in BNS patients.

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Authorship

JJC, GI and SPT designed the study. All the authors provided patient data. GI maintained the database. JJC and GI performed the analysis. JJC wrote the initial manuscript draft. All the authors reviewed and approved the final manuscript.

Disclosures

JJC received research funds from Abbvie, Beigene, Janssen and Pharmacyclics, and honoraria from Beigene, Janssen, Merck and Pharmacyclics. MV received honoraria from Janssen. CB has received research funds from Bayer, Janssen and Roche and honoraria from Gilead, Janssen, Pfizer and Roche. TAE received honoraria from Abbvie, Gilead and Janssen. JCC received honoraria from Bayer, Genentech, Janssen, Kite, Merck and Novartis. KHS received research funds from Abbvie, and honoraria from Amgen, BMS, Celgene, Janssen and Takeda. MLP received honoraria from Celgene, Merck and Pharmacyclics, and a family member of MLP received royalties from Juno and Seres. DT received research funds from Roche, and honoraria from Janssen and Roche. CST received research funding from Janssen and AbbVie, and honoraria from Janssen, Beigene, Pharmacyclics and AbbVie. LN has received honoraria from BMS. SPT received research funding from BMS and Pharmacyclics and honoraria from Pharmacyclics. GI, JP, SI, DS, AT and SMA have no conflict of interest to disclose.

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Table 1. Selected clinical characteristics and outcomes of 28 patients with Bing-Neel syndrome treated with ibrutinib

ID	Age WM diagnosis	Sex	Prior WM therapy	Age BNS diagnosis	Prior BNS therapy	Dose	At best response			Stopped ibrutinib	EFS months
							Symptomatic	Radiological	Cytological		
1	56	M	No	65	Yes	560	Improved	Improved	NA	No	23
2	60	F	No	60	No	560	Unchanged	Unchanged	Cleared	Yes	5
3	61	F	Yes	76	No	560	Improved	Improved	NA	No	23
4	72	M	Yes	78	No	420	Improved	Resolved	NA	No	27
5	48	F	No	49	Yes	560	Improved	Improved	Cleared	No	10
6	73	F	Yes	76	Yes	560	Unchanged	Improved	Cleared	No	4
7	65	M	Yes	75	Yes	560	Improved	Improved	Persistent	No	48
8	63	M	No	64	No	560	Improved	Improved	Persistent	No	6
9	61	F	No	61	No	560	Improved	Improved	Persistent	No	6
10	72	M	No	72	Yes	560	Improved	Improved	NA	No	3
11	53	M	Yes	65	Yes	420	Improved	Unchanged	Cleared	Yes	4
12	62	M	No	62	No	420	Improved	Unchanged	Persistent	No	13
13	56	M	Yes	65	No	420	Unchanged	Improved	NA	No	22
14	56	M	Yes	63	Yes	560	Resolved	NA	Cleared	No	10
15	52	M	Yes	78	Yes	420	Improved	NA	Cleared	Yes	1
16	49	F	No	50	Yes	560	Improved	NA	Persistent	No	8
17	55	F	Yes	59	No	560	Improved	NA	Persistent	Yes	4
18	64	M	No	64	Yes	420	Resolved	Resolved	Persistent	No	11
19	38	M	Yes	38	Yes	420	Resolved	Improved	NA	No	10
20	61	F	No	61	Yes	420	Unchanged	Improved	Persistent	Yes	8
21	67	F	Yes	71	No	420	Resolved	NA	NA	No	8
22	60	M	Yes	67	Yes	420	Resolved	Improved	Persistent	No	33
23	61	M	Yes	76	No	420	Improved	NA	Cleared	No	15
24	42	F	Yes	60	Yes	420	Improved	NA	NA	No	13
25	76	M	No	80	Yes	420	Improved	NA	NA	No	11
26	53	F	Yes	66	Yes	420	Improved	NA	Cleared	No	8
27	80	F	Yes	81	No	420	Improved	NA	NA	No	4
28	57	M	Yes	66	Yes	560	Improved	Improved	NA	No	13

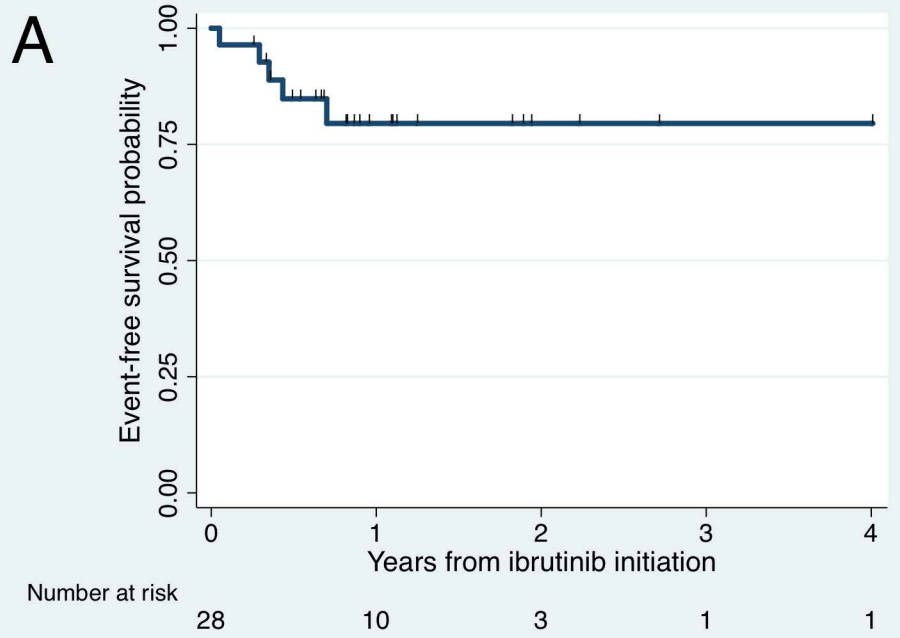
WM: Waldenstrom macroglobulinemia; BNS: Bing-Neel Syndrome; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; EFS: event-free survival (toxicity, progression or death); M: male; F: female; NA: not available

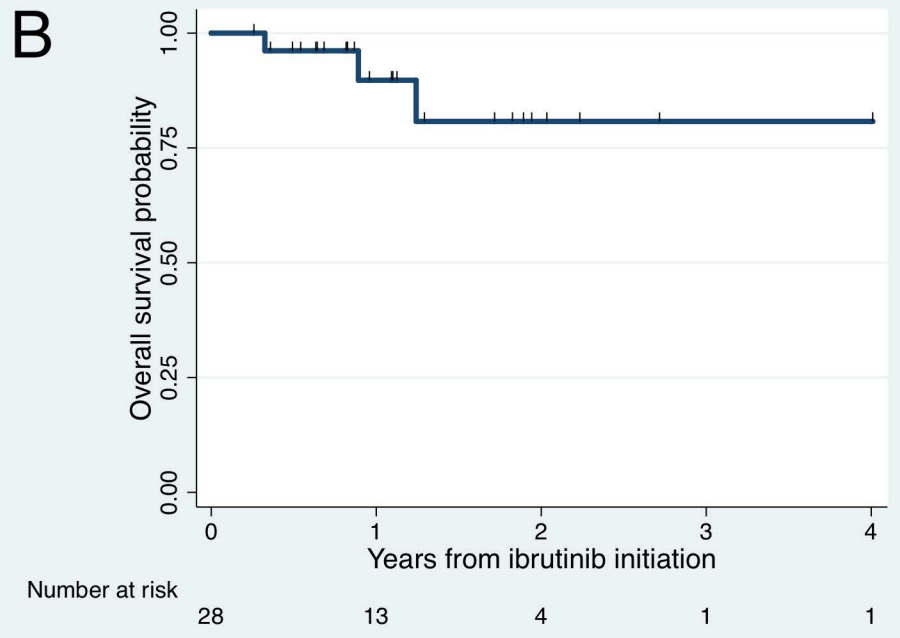
Table 2. Symptomatic, radiological and cytological responses in 28 patients with Bing-Neel syndrome treated with single agent ibrutinib

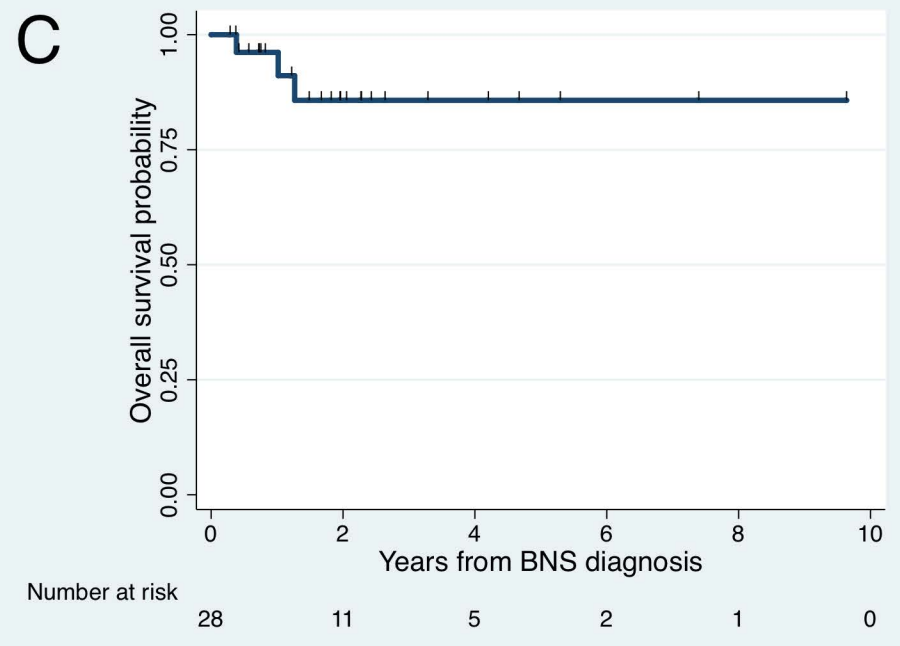
	3 months	6 months	12 months	Best response
Symptomatic				
Resolved	1/26 (4%)	3/20 (15%)	2/10 (20%)	5/28 (18%)
Improved	21/26 (81%)	15/20 (75%)	7/10 (70%)	19/28 (68%)
Unchanged	4/26 (15%)	2/20 (10%)	1/10 (10%)	4/28 (14%)
Radiological				
Resolved	0/15 (0%)	1/9 (11%)	2/8 (25%)	2/18 (11%)
Improved	9/15 (60%)	7/9 (78%)	6/8 (75%)	13/18 (72%)
Unchanged	6/15 (40%)	1/9 (11%)	0/8 (0%)	3/18 (17%)
Cytological				
Cleared	7/12 (58%)	2/7 (29%)	0/1 (0%)	8/17 (47%)
Persistent	5/12 (42%)	5/7 (71%)	1/1 (100%)	9/17 (53%)

Figure legends

Figure 1. Kaplan-Meier estimates in 28 patients with Bing-Neel syndrome treated with ibrutinib. (A) event-free survival on ibrutinib, (B) survival from ibrutinib initiation, and (C) survival from Bing-Neel syndrome diagnosis.


A
Event-free survival probability
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
Years from ibrutinib initiation
Number at risk
28
10
3
1
1


B
Overall survival probability
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
Years from ibrutinib initiation
Number at risk
28
13
4
1
1


C
Overall survival probability
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Years from BNS diagnosis
Number at risk
28
11
5
2
1
0

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