

Final Author's draft of a paper accepted for publication in the Journal of Hematology & Oncology 2017. DOI  
<https://doi.org/10.1186/s13045-017-0537-5>

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## **Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004)**

Michael Wang,<sup>1</sup> Stephen J. Schuster,<sup>2</sup> Tycel Phillips<sup>3</sup>, Izidore S. Lossos,<sup>4</sup> Andre Goy,<sup>5</sup> Simon Rule,<sup>6</sup> Mehdi Hamadani,<sup>7</sup> Nilanjan Ghosh,<sup>8</sup> Craig B. Reeder,<sup>9</sup> Evelyn Barnett,<sup>10</sup> Marie-Laure Casadebaig Bravo,<sup>11</sup> and Peter Martin<sup>12</sup>

<sup>1</sup>Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX, USA

<sup>2</sup>Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA

<sup>3</sup>University of Michigan, Ann Arbor, MI, USA

<sup>4</sup>University of Miami, Sylvester Comprehensive Cancer Center, Division of Hematology Oncology, Miami, FL, USA

<sup>5</sup>John Theurer Cancer Center at HUMC, Hackensack, NJ, USA

<sup>6</sup>Department of Haematology, Derriford Hospital and Plymouth University Medical School, Plymouth, UK

<sup>7</sup>Medical College of Wisconsin & CIBMTR, Milwaukee, WI, USA

<sup>8</sup>Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA

<sup>9</sup>Mayo Clinic Scottsdale/Phoenix, Scottsdale, AZ, USA

<sup>10</sup>Celgene Corporation, Summit, NJ, USA

<sup>11</sup>Celgene International Sàrl, Boudry, Switzerland

<sup>12</sup>Weill Cornell Medical College, New York, NY, USA

**Corresponding author:** Michael Wang, MD  
University of Texas MD Anderson Cancer Center  
1515 Holcombe Boulevard  
Houston, TX 77030  
Telephone: (713) 563-5067  
Fax: (713) 563-5067  
Email: [miwang@mdanderson.org](mailto:miwang@mdanderson.org)

1 **ABSTRACT**

2 The observational MCL-004 study evaluated outcomes in patients with  
3 relapsed/refractory mantle cell lymphoma who received lenalidomide-based therapy after  
4 ibrutinib failure or intolerance. The primary endpoint was investigator-assessed overall  
5 response rate based on the 2007 International Working Group criteria. Of 58 enrolled  
6 patients (median age, 71 years; range, 50-89), 13 received lenalidomide monotherapy,  
7 11 lenalidomide plus rituximab, and 34 lenalidomide plus other treatment. Most patients  
8 (88%) had received  $\geq 3$  prior therapies (median 4; range, 1-13). Median time from last  
9 dose of ibrutinib to the start of lenalidomide was 1.3 weeks (range, 0.1-21.7); 45% of  
10 patients had partial responses or better to prior ibrutinib. Primary reasons for ibrutinib  
11 discontinuation were lack of efficacy (88%) and ibrutinib toxicity (9%). After a median of  
12 two cycles (range, 0-11) of lenalidomide-based treatment, 17 patients responded (8  
13 complete responses, 9 partial responses), for a 29% overall response rate (95%  
14 confidence interval, 18%-43%) and a median duration of response of 20 weeks (95%  
15 confidence interval, 2.9-not available). Overall response rate to lenalidomide-based  
16 therapy was similar for patients with relapsed/progressive disease after previous  
17 response to ibrutinib (i.e.,  $\geq$ PR) versus ibrutinib-refractory (i.e.,  $\leq$ SD) patients (30% versus  
18 32%, respectively). The most common all-grade treatment-emergent adverse events after  
19 lenalidomide-containing therapy (n=58) were fatigue (38%) and cough, dizziness,  
20 dyspnea, nausea, and peripheral edema (19% each). At data cut-off, 28 patients have  
21 died, primarily due to mantle cell lymphoma. Lenalidomide-based treatment showed  
22 clinical activity, with no unexpected toxicities, in patients with relapsed/refractory mantle  
23 cell lymphoma who previously failed ibrutinib therapy.

1 **Trial registration number:** clinicaltrials.gov identifier NCT02341781

2 **Date of registration:** January 14, 2015

3 **Keywords:** ibrutinib failure, lenalidomide, mantle cell lymphoma.

4

## 1 **Background**

2 Mantle cell lymphoma (MCL) accounts for 3% to 6% of non-Hodgkin lymphomas and is  
3 generally characterized by cyclin D1 overexpression, and more recently by SOX11  
4 expression [1-3]. MCL is generally considered incurable with standard  
5 chemoimmunotherapy and approved targeted agents [4]. Although multiple molecular-  
6 based therapies have improved outcomes for patients with relapsed/refractory MCL, there  
7 is no established standard-of-care [5,6]. As summarized in a recent review, various  
8 chemoimmunotherapy regimens tested in small clinical trials in this setting have achieved  
9 high overall response rates (ORR) ranging from 58% to 93%, but progression-free  
10 survival (PFS) has been limited to <2 years [6], with reported overall survival (OS) as <3  
11 years [7-9].

12 Bortezomib, lenalidomide, and ibrutinib have received US Food and Drug  
13 Administration (FDA) approval for the treatment of relapsed/refractory MCL [10-12], and  
14 lenalidomide, ibrutinib, and temsirolimus are registered for this indication in the European  
15 Union [10,13,14]. Monotherapy activities with these targeted agents in phase II studies  
16 report ORRs ranging from 22% to 68%, complete response (CR) rates ranging from 2%  
17 to 21%, and median duration of response (DOR) ranging from 9.2 to 19.6 months [6]. In  
18 a randomized study comparing two targeted agents in patients with relapsed/refractory  
19 MCL, ibrutinib significantly reduced the risk of progressive disease (PD) or death  
20 compared with temsirolimus (hazard ratio [HR] 0.43; 95% confidence interval [CI], 0.32-  
21 0.58;  $P<0.0001$ ) [15]. After a median follow-up of 20 months, ibrutinib demonstrated an  
22 improved median PFS (14.6 versus 6.2 months;  $P<0.0001$ ), 2-year PFS (41% versus 7%;

1 *P* value not reported), ORR (72% versus 40%;  $P < 0.0001$ ), and CR rate (19% versus 1%;  
2 *P* value not reported) compared with temsirolimus.

3         Although these treatments have shown significant antitumor activity and are  
4 commonly used, primary and acquired resistance, intolerance, and drug-related toxicities  
5 are significant limitations of these treatment approaches. With ibrutinib in particular,  
6 recent studies have shown that MCL patients with primary or acquired resistance have  
7 poor clinical outcomes. A retrospective review of 31 patients with MCL who had PD  
8 following discontinuation of ibrutinib and received salvage chemoimmunotherapy showed  
9 an ORR of 32% with the first salvage regimen and an estimated 22% 1-year OS (median  
10 8.4 months) [16]. In another retrospective analysis, 114 heavily pretreated patients with  
11 MCL who developed PD while on ibrutinib (for a median treatment duration of 4.7 months)  
12 had a median OS of 2.9 months after discontinuing ibrutinib [17].

13         The oral immunomodulatory drug (IMiD) lenalidomide has demonstrated antitumor  
14 activity in preclinical studies of MCL, both as monotherapy and in combination with  
15 rituximab [18-21]. In clinical trials in patients with relapsed/refractory MCL and other non-  
16 Hodgkin lymphomas, lenalidomide demonstrated activity when used as a monotherapy  
17 [22-28] and in combination with rituximab ( $R^2$ ) [29, 30].

18         The objective of this retrospective, observational, multicenter MCL-004 study  
19 (NCT02341781) was to evaluate the clinical effectiveness and safety of lenalidomide  
20 used as monotherapy and in combination regimens to treat patients with MCL who had  
21 relapsed/progressed to an ibrutinib-containing treatment (i.e., had an initial response of  
22 PR or better), or who were refractory to (i.e., best response of SD or worse) or unable to  
23 tolerate ibrutinib.

## 1 **Patients and methods**

### 2 *Patients*

3 Harmonization E6 requirements (Good Clinical Practice) and ethical principles per the  
4 Declaration of Helsinki were followed. All aspects of the study were reviewed with the  
5 study investigators and staff; accuracy was confirmed through source data verification.

6 Inclusion criteria were: age  $\geq 18$  years; MCL verified by investigator review of a  
7 pathology report; at least 1 dose (cycle 1, day 1) of ibrutinib (monotherapy or  
8 combination); and ibrutinib failure defined as: relapse (CR followed by relapse at any  
9 time), PD (PR followed by PD at any time), refractory (PD, or stable disease [SD] followed  
10 by PD, while on ibrutinib), and/or intolerance (discontinuation of ibrutinib for reasons other  
11 than PD). Lenalidomide was not required to immediately follow ibrutinib.

### 12 *Study Design*

13 After identifying MCL patients treated with or intending to take lenalidomide following  
14 ibrutinib failure, an informed consent document was completed by the patient (family  
15 member/legal representative if patient was deceased), or a waiver was granted from the  
16 Institutional Review Board or Ethics Committee (IRB/EC) if consent was deemed not  
17 necessary for data collection. Patients were then enrolled into the clinical database, and  
18 data were extracted from medical charts including demographic information, relevant  
19 medical history, baseline disease characteristics, date of initial MCL diagnosis with  
20 pathology report, prior therapies (including treatment dates and best response), ibrutinib  
21 and lenalidomide treatment dates and outcome, copy of imaging reports, date of last  
22 follow-up/disease status, documentation of adverse events (AEs), and date/cause of

1 death. Patients were enrolled after meeting eligibility criteria. Non-retrospective data may  
2 have been collected when lenalidomide was ongoing at study entry.

3 The primary endpoint was ORR defined as achievement of CR or PR per 2007  
4 International Working Group (IWG) 2007 response criteria [31]. When initial assessments  
5 used IWG 1999 criteria (i.e., unconfirmed CR [32]), the corresponding response per IWG  
6 2007 was changed to PR. Patients without a response evaluation or had an unknown  
7 response were considered non-responders. The secondary endpoint was DOR (time from  
8 initial response to lenalidomide-based therapy of  $\geq$ PR to relapse/PD/death, whichever  
9 occurred first). Responding patients without PD/death at analysis were censored at the  
10 last assessment date.

### 11 *Response and Safety Assessments*

12 Time-to-event data were estimated using the Kaplan-Meier method [33]. Planned  
13 analyses were conducted for MCL subgroups of refractory (best response to ibrutinib of  
14 SD or worse), relapsed/PD (initial response to ibrutinib of  $\geq$ PR followed by PD), and those  
15 unable to tolerate ibrutinib (any reason other than lack of efficacy).

16 Available records of treatment-emergent AEs (TEAEs) with an onset date after  
17 lenalidomide initiation through 28 days after the last lenalidomide dose, regardless of  
18 causality, were analyzed in the safety population. AEs were classified according to the  
19 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events  
20 (CTCAE) version 4.03.

### 21 *Statistical Analysis*

1 All efficacy evaluations were conducted in the eligible patients. Patients were grouped by  
2 first type of lenalidomide treatment received: single agent, in combination with rituximab,  
3 or in combination with other agents. The response rate probability was estimated using  
4 the proportion of responding patients with an exact two-sides 95% CI; a sample size of  
5 30 patients would allow a two-sided 95% CI (lower boundary of 10%) for an expected  
6 proportion of 25%.

## 7 **Results**

### 8 *Patient Characteristics*

9 MCL patients from March 1, 2009 to April 12, 2016 who were treated with lenalidomide  
10 following ibrutinib therapy were enrolled. The data cutoff for all patients was November 1,  
11 2016. The study enrolled 58 patients at a total of 11 study sites, including 10 sites in the  
12 United States and 1 site in England (Supplemental Table 1). Seven patients signed  
13 informed consent forms (one patient signed consent prior to initiating lenalidomide  
14 treatment), and 51 patients had IRB/EC waivers. Thirteen patients were treated with  
15 lenalidomide monotherapy, 11 with lenalidomide plus rituximab, and 34 with other  
16 lenalidomide combinations (Supplemental Table 2). Two patients initially identified for  
17 analysis were excluded from this observational cohort because they did not meet all  
18 eligibility criteria (one patient treated with lenalidomide plus rituximab had not relapsed  
19 while on ibrutinib, and one patient was not treated with lenalidomide); these 2 patients  
20 are not included in the overall enrolled set of 58 patients.

21 Patients had a median age of 71 years (range, 50-89), and 71% were age  $\geq$ 65  
22 years (Table 1). 48% of patients had an Eastern Cooperative Oncology Group  
23 performance status of 0-1, 29% had high tumor burden, and 14% had bulky disease ( $\geq$ 7



1 cm). The Mantle Cell International Prognostic Index (MIPI) score could not be derived for  
2 most patients due to a lack of the required data to complete appropriate calculations for  
3 30 patients (i.e., 52% missing data for MIPI; Ki-67 data were not collected).

4 Patients had received a median of four prior lines of systemic anti-lymphoma  
5 therapy (range, 1-13), 88% had three or more prior therapies, and 79% had received  
6 ibrutinib as monotherapy (Table 2). Most patients (60%) had lenalidomide-containing  
7 therapy as their next line of therapy, and 40% patients had  $\geq 1$  line(s) of other therapy  
8 preceding the lenalidomide regimen. Median duration of ibrutinib treatment was 4.3  
9 months (range, 0.5-47.6). 88% patients discontinued ibrutinib treatment for one or more  
10 reason: due to relapse/PD (n=27) and/or refractoriness (n=25), six patients discontinued  
11 due to toxicity, and one patient completed ibrutinib as planned but had relapsed/PD at the  
12 end of ibrutinib treatment. Besides ibrutinib, the most common previous systemic  
13 therapies were rituximab (97%), cyclophosphamide (84%), glucocorticoids (78%),  
14 vincristine (78%), doxorubicin (72%), bendamustine (57%), and cytarabine (52%)  
15 (Supplemental Table 3; note that multiple treatment names could be used to collect this  
16 information). The median time from last dose of ibrutinib to first dose of lenalidomide was  
17 1.3 weeks (range, 0.1-21.7).

#### 18 *Efficacy*

19 Among the 58 patients, the median duration of treatment was 8.4 weeks for single agent  
20 lenalidomide and 7.4 weeks for lenalidomide-containing combination therapy (Table 4).  
21 Eight patients achieved a CR and 9 achieved a PR with lenalidomide-based therapy, for  
22 an ORR of 29% (95% CI, 18%-43%; Table 3), which exceeded the predefined lower  
23 boundary of the 95% confidence threshold of 10% ORR. Seven of the 8 patients with CR

1 had CT ± PET/CT assessments. Two of the 13 patients (15%) who had single-agent  
2 lenalidomide (fourth line of therapy for both) reported a best response of relapse/PD to  
3 ibrutinib; 3/13 (23%) patients on single-agent lenalidomide had unknown response status  
4 with 8/13 (62%) reporting relapse/PD.

5         The median DOR for responders was 20 weeks (95% CI, 2.9 to not reached); of  
6 the 17 responders, 14 (82%; 7 CR and 7 PR) were censored from the DOR analysis due  
7 to lack of follow-up data on PD or death. At the last available assessment of the 14  
8 censored patients: 3 were ongoing; 3 had completed lenalidomide treatment as planned;  
9 and 8 patients discontinued lenalidomide treatment early (withdrew consent [n=1], patient  
10 decision [n=1], enrolled in a clinical trial for oral treatment [n=1], started other lines of  
11 treatment [n=3; because of lung cancer, physician's decision, or bone marrow transplant],  
12 and toxicity [n=2]). One of the censored patients who had a first response of PR and best  
13 response of CR had the last censored DOR at 25 weeks before stopping therapy. For the  
14 three uncensored patients, two had a best response of PR and one had CR, with an  
15 estimated DOR of 2.9, 19.7, and 16.4 weeks, respectively. Univariate analysis showed a  
16 median DOR of 16 weeks (95% CI, 2.9-19.7) in the 3 uncensored patients (14 patient  
17 responders were censored; total of 17 responders).

### 18 *Response by Subgroup Analysis*

19 Patients with MCL refractory to ibrutinib versus those who relapsed/progressed on or  
20 following ibrutinib had similar ORRs of 32% vs 30%, respectively (Fig 1); however, the  
21 CR rates were not similar (8% vs 22%). Median DOR was 20 weeks (CI 95%, 2.9-20) for  
22 the ibrutinib-refractory group and not available for the relapsed/PD group. There was 1  
23 PR (17%) among the 6 patients who were ibrutinib intolerant; all 6 patients were treated

1 with lenalidomide within 6 months of stopping ibrutinib therapy. Of 48 patients who  
2 tolerated ibrutinib therapy, 7 had CRs and 8 had PRs, a 31% ORR, and the median DOR  
3 was 20 weeks.

#### 4 *Safety*

5 Overall, patients received a median of 2 (range, 0-11) cycles of lenalidomide-based  
6 treatment. Most patients received lenalidomide 10-25 mg/day on days 1-21 of each 28-  
7 day cycle. As of the cut-off date of November 1, 2016, 54 patients had discontinued  
8 lenalidomide-based therapy and four patients continue to receive lenalidomide (3  
9 censored for efficacy analyses), one in combination with weekly  
10 bortezomib/dexamethasone/rituximab, two in combination with weekly rituximab, and one  
11 in combination with weekly obinutuzumab. The primary reasons for lenalidomide  
12 treatment discontinuation were lack of efficacy (n=27); toxicity (n=10); other reasons  
13 (n=9), such as initiation of another therapy (e.g., based on physician or patient choice) or  
14 trial (also an oral therapy), undergoing stem cell transplantation, or primary  
15 clinician/patient decision to stop therapy; completion of lenalidomide treatment (n=5); and  
16 missing data (n=3).

17 Of the 58 patients analyzed for safety, 48 (83%) had one or more TEAE during  
18 lenalidomide treatment. Twenty (34%) patients had at least one serious TEAE  
19 (lenalidomide alone 23%; lenalidomide+rituximab 36%; lenalidomide+others 38%). The  
20 most frequently reported serious TEAEs of any grade were febrile neutropenia (n=4; 7%),  
21 hypotension (7%), deep vein thrombosis (DVT) (n=3; 5%), pneumonia (5%),  
22 pancytopenia (5%), fall (5%), acute kidney injury (5%), dyspnea (n=2; 3%), sepsis (3%),  
23 and respiratory failure (3%). Overall, 9 (16%) patients had at least one TEAE leading to

1 dose discontinuation (lenalidomide alone 8%; lenalidomide+rituximab 18%;  
2 lenalidomide+others 18%). These TEAEs included pancytopenia, thrombocytopenia, and  
3 rash, each experienced by two patients (3%), and anemia, febrile neutropenia,  
4 neutropenia, sepsis, fall, squamous cell lung carcinoma, dyspnea, pleural effusion, and  
5 orthostatic hypotension, each experienced by one patient (2%). The most common all-  
6 grade TEAEs were fatigue, cough, dizziness, dyspnea, nausea, peripheral edema,  
7 anemia, rash, thrombocytopenia, and neutropenia (Table 5).

8         As of the cut-off date, 28 (48%) patients had died, 12 (21%) during treatment with  
9 lenalidomide, and 15 (26%) during follow-up (1 unknown). Overall, 20 (34%) patients died  
10 from malignant disease (i.e., MCL) or its complications, five from unknown causes (not  
11 assessable or insufficient data), one reported another cause of end-stage renal disease,  
12 and two due to AEs. Of the two patients who died due to AEs, the first patient included a  
13 68-year-old man in the lenalidomide-alone group who died during treatment (83 days after  
14 the first lenalidomide dose). This patient had a PR two months after lenalidomide initiation  
15 but died due to a pulmonary embolism, suspected to be related to lenalidomide therapy,  
16 as well as had incidences of other grade 5 AEs (DVT and cardiac arrest). Although this  
17 patient was receiving aspirin, therapy was stopped during study admission. For most  
18 patients, it is not known if the patients received antithrombotic treatment, since  
19 concomitant treatments were not part of the collected data. The second patient who died  
20 due to an AE was a 71-year-old man who received one treatment cycle of lenalidomide  
21 in combination with ibrutinib, rituximab, bortezomib, and dexamethasone. This second  
22 patient died while on study treatment (25 days after the first dose of lenalidomide)

1 because of progression of MCL (which included acute kidney injury, lactic acidosis,  
2 respiratory failure, hypotension).

### 3 **Discussion**

4 This multicenter observational study examined outcomes with lenalidomide treatment in  
5 patients with MCL who had relapsed or progressed after or during ibrutinib therapy or  
6 were intolerant to ibrutinib. Most patients had received three or more prior lines of  
7 treatment and had discontinued ibrutinib due to a lack of efficacy. Most patients (79%)  
8 had previously received ibrutinib as a monotherapy. The ORR of 45% and median DOR  
9 of 4.3 months was lower compared to previous clinical trials of ibrutinib monotherapy for  
10 relapsed/refractory MCL; there was also a higher number of prior regimens in the current  
11 study [34,35]. These factors suggest a higher-risk cohort and a potential negative impact  
12 on response to subsequent therapy, including lenalidomide. Nonetheless, lenalidomide-  
13 based treatment demonstrated meaningful clinical activity in this difficult-to-treat patient  
14 population, as demonstrated by a 29% ORR and 14% CR, with a 20-week (95% CI, 2.9  
15 to not available) median DOR. For the DOR analysis, it should be noted that because  
16 82% of responders were censored, the data should be interpreted with caution. With no  
17 new safety signals identified, the safety profile in these patients matched the well-  
18 established safety shown in multiple studies of lenalidomide monotherapy [22-28].

19 Prior studies have shown that lenalidomide treatment had significant clinical  
20 activity in relapsed/refractory MCL. The MCL-001 EMERGE study reported a 28% ORR  
21 (including 8% CR/CR unconfirmed) and 16.6-months DOR with lenalidomide  
22 monotherapy in 134 patients with relapsed/refractory MCL after bortezomib treatment.  
23 Patients from MCL-001 had received a median of four prior treatment regimens, and 88%

1 had been treated with at least three prior systemic antilymphoma therapies [26]. A UK  
2 study reported a 31% ORR, 8% CR, and 22.2-month median DOR with single-agent  
3 lenalidomide (6 cycles at 25 mg/day followed by 15 mg/day lower maintenance dose) in  
4 26 patients with relapsed/refractory MCL who had received a median of three prior  
5 systemic therapies [25]. The lower DOR of <5 months in the current study could be a  
6 result of ibrutinib resistance. In the randomized MCL-002 (SPRINT) study of 254 patients  
7 with relapsed/refractory MCL, the lenalidomide monotherapy group showed higher ORR  
8 (40% versus 11%;  $P<0.001$ ) compared with investigator's choice (monotherapy with  
9 chlorambucil, cytarabine, gemcitabine, fludarabine, or rituximab), respectively [28].  
10 Median DOR was 16.1 months for lenalidomide and 10.4 months for the investigator's  
11 choice group. Lenalidomide in combination with rituximab ( $R^2$ ) has also shown activity in  
12 relapsed/refractory MCL. In a phase I/II dose-finding study  $R^2$  was well tolerated in MCL  
13 and among 44 patients in phase II: ORR was 57% (CR 36%) and DOR was 18.9 months  
14 [30]. A phase II study of iNHL or MCL showed lenalidomide monotherapy followed by  $R^2$   
15 overcame rituximab resistance [29]. In the 14 patients with MCL, ORR after lenalidomide  
16 monotherapy and  $R^2$  was 55% for each; DOR to  $R^2$  was 22.1 months. Since responses  
17 to lenalidomide in the post-ibrutinib setting are not durable, early referral for allogeneic  
18 hematopoietic stem-cell transplantation (allo-HCT) should be strongly considered for  
19 responding MCL patients without advanced comorbidities [36-38].

20       There are several limitations to the study, including the retrospective nature of  
21 chart review and limited follow-up, which contribute to censoring patients for time-to-event  
22 statistics such as DOR. The prevalence of AEs may also be underestimated due to  
23 possible under-reporting or other uncontrolled factors such as pre-existing events. Safety

1 summary tables were generated with the expectation of missing data (e.g., grade,  
2 treatment-relatedness, seriousness) that might limit the safety analysis. Because of the  
3 heterogeneity of regimens combined with lenalidomide, it is difficult to confidently discern  
4 the amount of response due to lenalidomide versus the other therapies used in  
5 combination, apart from two responses to lenalidomide monotherapy. The two  
6 responders to lenalidomide monotherapy represented only 12% of the 17 patients who  
7 responded on lenalidomide-containing therapy, further complicating delineation of the  
8 effects of lenalidomide with or without other therapies. It would also be beneficial to  
9 deduce which patients were previously refractory to rituximab.

10 As ibrutinib is being used more frequently for patients with MCL, the opportunity  
11 now arises to assess the role of other therapies following ibrutinib. Because multiple  
12 studies have shown that MCL patients with ibrutinib failure demonstrate poor outcomes  
13 with subsequent therapy [16, 17], it is critical to identify therapies that may provide activity  
14 in these patients. Multiple second-generation BTK inhibitors are being investigated to  
15 evaluate possible improvements in target specificity, potency, and tolerability through this  
16 pathway [39, 40]. Results from this observational study indicate that lenalidomide-based  
17 therapy has clinically significant activity as a monotherapy and in combination regimens  
18 to treat heavily pretreated patients with refractory or relapsed MCL after ibrutinib therapy  
19 or who cannot tolerate ibrutinib and thus, lenalidomide addresses an unmet medical need  
20 and widens the therapeutic options in a difficult-to-treat patient population.

21

1 **Acknowledgements**

2 Editorial support was provided by Bio Connections LLC and funded by Celgene  
3 Corporation. The authors directed development of the manuscript and are fully  
4 responsible for all content and editorial decisions.

5

6 **Funding**

7 This study was supported by Celgene Corporation, Summit, NJ.

8

9 **Availability of data and materials**

10 The material generated or analyzed during this study are included within the article and  
11 its supplementary information files.

12

13 **Author contributions:** All authors share equal responsibility for the study and provided  
14 equal contribution.

15

16 **Competing interests**

17 MW reports research grants, honoraria, and nonfinancial support from Janssen, Acerta  
18 Pharma, Pharmacyclics, and Celgene; research grants and nonfinancial support from  
19 Kite Pharma; research grants from Juno Therapeutics, Amgen, Karyopharm  
20 Therapeutics, Asana BioSciences, BeiGene, Novartis, Oncoceutics, Oncternal  
21 Therapeutics, and Karus; and honoraria from BioInvent International and Adienne  
22 Pharma & Biotech.



- 1 SJS reports research funding from Celgene during the conduct of the study.
- 2 IL and TP declare that they have no competing interests.
- 3 AG reports research funding for the institution from and was a consultant for Celgene,
- 4 Genentech, Pharmacyclics/J&J; and received honoraria from Celgene,
- 5 Pharmacyclics/J&J, Acerta, and Takeda.
- 6 SR reports personal fees from Roche, Janssen, AstraZeneca, Celgene, Napp, AbbVie,
- 7 and MSD.
- 8 MH was on the Speaker Bureau for Celgene and Sanofi; received honorarium from
- 9 Celgene; received research funding from Takeda and Sanofi; and was a consultant for
- 10 Janssen R&D.
- 11 NG reports Speaker's Bureau and consultancy for Celgene, Gilead, and AbbVie;
- 12 Speaker Bureau, consultancy and research funding for PCYC and Janssen;
- 13 consultancy and research funding for SGN; research funding for Genentech; and
- 14 consultancy and research funding for TG Therapeutics.
- 15 CBR reports research funding from Celgene, Millennium, and Novartis.
- 16 MLCB and EB are employees of Celgene Corporation.
- 17 PM reports personal consulting fees from Celgene and Janssen/Pharmacyclics.
- 18

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37

1 **Table 1** Patient characteristics at study entry.

Characteristic	L (n=13)		L+R (n=11)		L+Other (n=34)		Overall (N=58)	
	No	%	No	%	No	%	No	%
Median age, years (range)	67 (54-83)		70 (58-84)		71 (50-89)		71 (50-89)	
≥65	6	46	9	82	26	76	41	71
Sex								
Male	11	85	8	73	25	74	44	76
Female	2	15	3	27	9	26	14	24
ECOG PS								
0-1	7	54	5	45	16	47	28	48
2-4	3	23	1	9	4	12	8	14
Missing	3	23	5	45	14	41	22	38
Tumor burden*								
High	4	31	1	9	12	35	17	29
Low	1	8	5	45	13	38	19	33
Missing	8	62	5	45	9	26	22	38
Bulky disease†								
Yes	2	15	0	0	6	18	8	14
No	2	15	6	55	17	50	25	43
Missing	9	69	5	45	11	32	25	43
Time from diagnosis to first lenalidomide dose, months								
Median	58		47		46		49	
Range	15-144		6-105		4-214		4-214	
Time from end of last prior antilymphoma therapy to first dose of lenalidomide, weeks								
Median	0.7		0.3		0.7		0.7	
Range	0.1-3.5		0.1-21.7		0.1-12.6		0.1-21.7	

2 ECOG PS: Eastern Cooperative Oncology Group performance status; L: lenalidomide;

3 L+R: lenalidomide plus rituximab.

4 \*High tumor burden is defined as at least one lesion ≥5 cm in diameter or three lesions  
5 ≥3 cm in diameter.<sup>22</sup>

6 †Bulky disease is defined as at least one lesion ≥7 cm in the longest diameter.<sup>22</sup>

7  
8

1 **Table 2** Treatment history of enrolled patients

	L (n=13)		L+R (n=11)		L+Other (n=34)		Overall (N=58)	
	No	%	No	%	No	%	No	%
No. of prior antilymphoma treatment regimens								
Median	4		3		4		4	
Range	3-7		2-8		1-13		1-13	
No. of prior antilymphoma therapies								
1	0	0	0	0	1	3	1	2
2	0	0	4	36	2	6	6	10
3	5	38	3	27	10	29	18	31
≥4	8	62	4	36	21	62	33	57
Missing	0	0	0	0	0	0	0	0
Type of ibrutinib treatment								
Combination regimen	1	8	1	9	10	29	12	21
Monotherapy	12	92	10	91	24	71	46	79
Ibrutinib status at study inclusion								
Relapse/PD	6	46	2	18	15	44	23	40
Refractory	2	15	8	73	15	44	25	43
Intolerant	3	23	0	0	3	9	6	10
Missing	2	15	1	9	1	3	4	7
Duration of ibrutinib treatment, months								
Median	4.8		3.9		4.3		4.3	
Range	1.2-13.9		2.0-16.6		0.5-47.6		0.5-47.6	
Best response on ibrutinib								
CR	2	15	0	0	6	18	8	14
PR	5	38	2	18	11	32	18	31
SD	0	0	1	9	0	0	1	2
Relapse/PD	5	38	8	73	15	44	28	48
Unknown	1	8	0	0	2	6	3	5
Primary reason for ibrutinib discontinuation								
Lack of efficacy	9	69	11	100	31	91	51	88
Toxicity to ibrutinib	3	23	0	0	2	6	5	9
Toxicity attribution unknown	0	0	0	0	1	3	1	2
Completed ibrutinib treatment	1	8	0	0	0	0	1	2
Time from end of last dose of ibrutinib to first dose of lenalidomide, weeks*								
Median	1.4		0.4		1.3		1.3	

	<b>L (n=13)</b>		<b>L+R (n=11)</b>		<b>L+Other (n=34)</b>		<b>Overall (N=58)</b>	
	<b>No</b>	<b>%</b>	<b>No</b>	<b>%</b>	<b>No</b>	<b>%</b>	<b>No</b>	<b>%</b>
Range	0.1-7.4		0.1-21.7		0.1-16.8		0.1-21.7	

- 1 CR: complete response; L: lenalidomide; L+R: lenalidomide plus rituximab; PD:
- 2 progressive disease; PR: partial response; SD: stable disease.
- 3 \*Time from last dose of ibrutinib to first dose of lenalidomide (weeks) is calculated as:
- 4 (lenalidomide first dose date - end date of ibrutinib + 1) / 7.
- 5

1 **Table 3** Efficacy outcomes with lenalidomide in patients with MCL after ibrutinib failure  
 2 or intolerance

Outcome	L (n=13)		L+R (n=11)		L+Other* (n=34)		Overall (N=58)	
	No	%	No	%	No	%	No	%
Best response by investigator's assessment								
ORR	2	15	3	27	12	35	17	29
95% CI	2%-45%		6%-61%		20%-54%		18%-43%	
CR	0	0	1	9	7	21	8	14
PR	2	15	2	18	5	15	9	15
SD	0	0	1	9	3	9	4	7
Relapse/PD	8	62	3	27	16	47	27	47
Unknown	3	23	2	18	3	9	8	14
Missing	0	0	2	18	0	0	2	3
Duration of response, weeks								
KM Median	3		20		NA		20	
95% CI	NA to NA		NA to NA		16.4 to NA		2.9 to NA	

3 CI: confidence interval; CR: complete response; KM: Kaplan-Meier; L: lenalidomide;  
 4 L+R: lenalidomide plus rituximab; MCL: mantle cell lymphoma; NA: not applicable; PD:  
 5 progressive disease; PR: partial response; SD: stable disease.

6 \*Supplemental Table 2 lists the other treatments.

7



1 **Table 4** Lenalidomide treatment exposure (safety population)

	<b>L (n=13)</b>	<b>L+R (n=11)</b>	<b>L+Other (n=34)</b>	<b>Overall (N=58)</b>
Lenalidomide treatment duration, weeks				
Median	8.4	14.0	7.0	8.4
Range	0.4 to 30.0	0.9 to 37.9	1.1 to 77.9	0.4 to 77.9
Number of lenalidomide cycles				
Median	2.0	2.0	1.0	2.0
Range	1.0 to 7.0	1.0 to 9.0	0.0 to 11.0	0.0 to 11.0
Duration of other therapy combined with lenalidomide, weeks				
Median	NA	8.3	7.2	7.4
Range	NA	0.1 to 35.9	0.7 to 77.7	0.1 to 77.7

2 L: lenalidomide; L+R: lenalidomide plus rituximab; NA: not applicable.

3

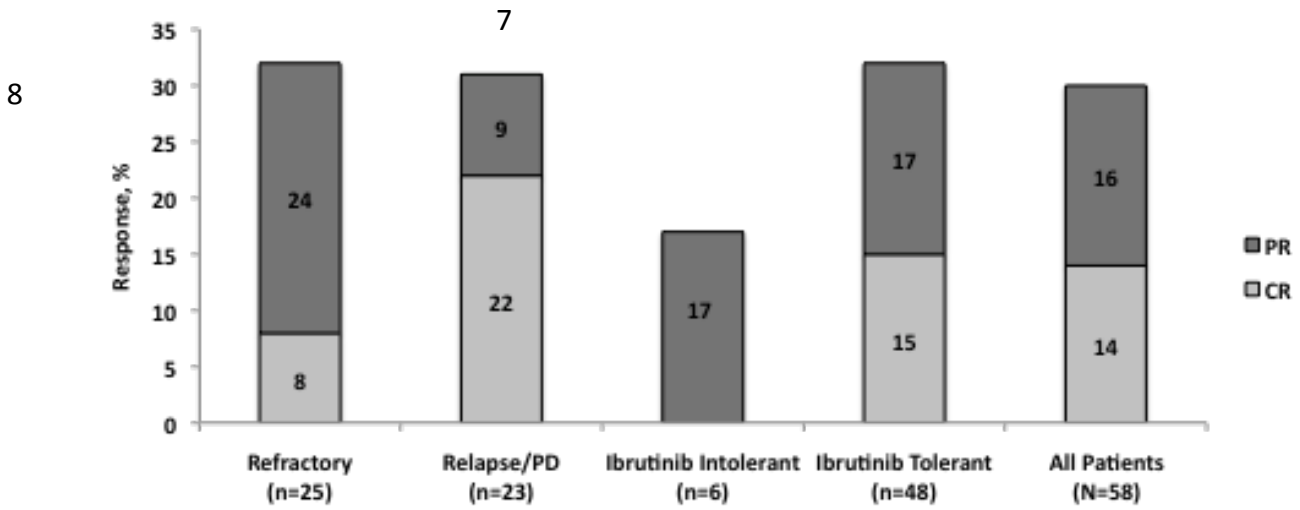
1 **Table 5** Documented treatment-emergent all-grade adverse events in ≥10% of patients  
 2 (safety population)

	L (n=13)		L+R (n=11)		L+Other (n=34)		Overall (N=58)	
	No	%	No	%	No	%	No	%
<b>Hematologic</b>								
Anemia	2	15	3	27	5	15	10	17
Thrombocytopenia	1	8	1	9	7	21	9	16
Neutropenia	1	8	1	9	6	18	8	14
Pancytopenia	1	8	3	27	3	9	7	12
Febrile neutropenia	0	0	0	0	6	18	6	10
<b>Nonhematologic</b>								
Fatigue	4	31	4	36	14	41	22	38
Nausea	2	15	2	18	7	21	11	19
Dizziness	2	15	2	18	7	21	11	19
Dyspnea	2	15	3	27	6	18	11	19
Peripheral edema	0	0	2	18	9	26	11	19
Rash	2	15	1	9	7	21	10	17
Cough	1	8	3	27	7	21	11	19
Decreased appetite	2	15	0	0	5	15	7	12
Diarrhea	0	0	1	9	7	21	8	14
Headache	3	23	1	9	2	6	6	10
Pyrexia	1	8	0	0	5	15	6	10
Vomiting	0	0	2	18	4	12	6	10
Constipation	0	0	0	0	6	18	6	10
<b>Laboratory investigations</b>								
Platelet count decreased	2	15	1	9	3	9	6	10
White blood cell count decreased	1	8	1	9	4	12	6	10

3 L: lenalidomide; L+R: lenalidomide plus rituximab.  
 4  
 5  
 6

1 **Figure Legend**

2 **Fig. 1** Best evaluable response\* to lenalidomide by subgroup. Subgroups include those  
3 of refractory versus relapsed/progressive disease, intolerant versus tolerant to ibrutinib,  
4 and all patients. CR: complete response; PD: progressive disease; PR: partial  
5 response. \*Response data were missing or unknown for 3 refractory, 5 relapse/PD, 0  
6 ibrutinib intolerant, 8 ibrutinib tolerant, and 10 patients overall.



1 **Additional Supplemental Files**

2

3 **Supplemental Table 1** Number of patients per study site

4

	L (n=13)		L+R (n=11)		L+Other (n=34)		Overall (N=58)	
	No	%	No	%	No	%	No	%
Univ. of Texas MDACC	0	0	3	27	16	47	19	33
Weill Cornell Medical College	3	23	3	27	7	21	13	22
Univ. of Michigan Comprehensive Cancer Center	3	23	1	9	1	3	5	9
Sylvester Comprehensive Cancer Center	2	15	2	18	1	3	5	9
Froedtert and The Medical College of Wisconsin	1	8	0	0	3	9	4	7
Derriford Hospital	3	23	0	0	1	3	4	7
Hackensack Univ. Medical Center	0	0	0	0	3	9	3	5
Univ. of Pennsylvania	0	0	0	0	2	6	2	3
Mayo Clinic Scottsdale	1	8	0	0	0	0	1	2
Levine Cancer Center	0	0	1	9	0	0	1	2
Non Engaged-First Health of the Carolinas	0	0	1	9	0	0	1	2

5 L: lenalidomide; L+R: lenalidomide plus rituximab; MDACC: MD Anderson Cancer  
 6 Center; Univ.: University.

7

1 **Supplemental Table 2** Lenalidomide combination treatments for L+Other group (n=34)  
2

<b>Lenalidomide Plus:</b>	<b>No</b>
Bortezomib/dexamethasone/rituximab	6
Bortezomib/dexamethasone/ibrutinib/rituximab	3
Carfilzomib/dexamethasone/rituximab	3
Bortezomib/rituximab	2
Dexamethasone/bortezomib	2
Dexamethasone/ibrutinib/obinutuzumab	2
Dexamethasone/rituximab	2
Ibrutinib	2
Rituximab/vincristine	2
Bendamustine	1
Bendamustine/rituximab/vincristine	1
Bortezomib	1
Bortezomib/dexamethasone/ibrutinib	1
Cytarabine	1
Dexamethasone/cyclophosphamide	1
Dexamethasone/everolimus/ibrutinib	1
Dexamethasone/obinutuzumab	1
Obinutuzumab	1
Prednisone/rituximab	1

3  
4

1 **Supplemental Table 3** Prior systemic anti-lymphoma therapies ( $\geq 10\%$  of patients;  
2 N=58)\*  
3

<b>Description</b>	<b>No (%)</b>
<b>Protein kinase inhibitors</b>	<b>58 (100)</b>
Ibrutinib	58 (100)
Palbociclib	8 (14)
<b>Monoclonal antibodies</b>	<b>56 (97)</b>
Rituximab	56 (97)
<b>Alkylating agents</b>	<b>56 (97)</b>
Cyclophosphamide	49 (84)
Bendamustine	33 (57)
Ifosfamide	7 (12)
<b>Glucocorticoids</b>	<b>45 (78)</b>
Dexamethasone	29 (50)
Prednisone	17 (29)
Prednisolone	7 (12)
<b>Vinca alkaloids and analogues</b>	<b>45 (78)</b>
Vincristine/vincristine sulfate	45 (78)
<b>Anthracyclines and related substances</b>	<b>42 (72)</b>
Doxorubicin/doxorubicin hydrochloride	42 (72)
<b>Other antineoplastic agents</b>	<b>30 (52)</b>
Bortezomib	29 (50)
<b>Pyrimidine analogues</b>	<b>30 (52)</b>
Cytarabine	30 (52)
<b>Folic acid analogues</b>	<b>24 (41)</b>
Methotrexate	24 (41)
<b>Podophyllotoxin derivatives</b>	<b>14 (24)</b>
Etoposide	14 (24)
<b>Platinum compounds</b>	<b>11 (19)</b>
Cisplatin	8 (14)

4 \*2 patients total (1 each in the L+R and L+Other group) had received prior lenalidomide  
5 therapy.  
6  
7