

# Lenalidomide in Pretreated Mantle Cell Lymphoma Patients: An Italian Observational Multicenter Retrospective Study in Daily Clinical Practice (the Lenamant Study)

VITTORIO STEFONI,<sup>a</sup> CINZIA PELLEGRINI,<sup>a</sup> ALESSANDRO BROCCOLI,<sup>a</sup> LUCA BALDINI,<sup>b</sup> MONICA TANI,<sup>c</sup> EMANUELE CENCINI,<sup>d</sup> AMALIA FIGUERA,<sup>e</sup> MICHELA ANSUINELLI,<sup>f</sup> ELISA BERNOCCHI,<sup>g</sup> MARIA CANTONETTI,<sup>h</sup> MARIA CHRISTINA COX,<sup>i</sup> FILIPPO BALLERINI,<sup>j</sup> CHIARA RUSCONI,<sup>k</sup> CARLO VISCO,<sup>l</sup> LUCA ARCAINI,<sup>m</sup> ANGELO FAMA,<sup>n</sup> ROBERTO MARASCA,<sup>o</sup> STEFANO VOLPETTI,<sup>p</sup> ALESSIA CASTELLINO,<sup>q</sup> CATELLO CALIFANO,<sup>r</sup> MARINA CAVALIERE,<sup>s</sup> GUIDO GINI,<sup>t</sup> ANNA MARINA LIBERATI,<sup>u</sup> GERARDO MUSURACA,<sup>v</sup> ANNA LUCANIA,<sup>w</sup> GIUSEPPINA RICCIUTI,<sup>x</sup> LISA ARGNANI,<sup>a</sup> PIER LUIGI ZINZANI<sup>a</sup>

<sup>a</sup>Institute of Hematology, University of Bologna, Bologna, Italy; <sup>b</sup>Division of Hematology, Fondazione IRCCS Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy; <sup>c</sup>Unit of Hematology, Santa Maria delle Croci Hospital, Ravenna, Italy; <sup>d</sup>Hematology Unit, University of Siena, Siena, Italy; <sup>e</sup>Division of Hematology, AOU Policlinico-Vittorio Emanuele, Catania, Italy; <sup>f</sup>Hematology, Department of Cellular Biotechnologies and Hematology, 'Sapienza' University, Rome, Italy; <sup>g</sup>Division of Hematology - SS. Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; <sup>h</sup>UOC Onco-Hematology Policlinico Tor Vergata, Rome, Italy; <sup>i</sup>Hematology, Sant'Andrea Hospital, La Sapienza University, Rome, Italy; <sup>j</sup>IRCCS A.O.U. San Martino-IST, Genoa, Italy; <sup>k</sup>Division of Hematology, Niguarda Cancer Center, Milan, Italy; <sup>l</sup>Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; <sup>m</sup>Department of Hematology-Oncology, Fondazione IRCCS Policlinico San Matteo & Department of Molecular Medicine, University of Pavia, Pavia, Italy; <sup>n</sup>Hematology-Arcispedale S.Maria Nuova IRCCS, Reggio Emilia, Italy; <sup>o</sup>Department of Medical Sciences, Section of Hematology, University of Modena and Reggio Emilia, Modena, Italy; <sup>p</sup>Chair of Hematology, DRMM, University of Udine, Udine, Italy; <sup>q</sup>A.O. Città della Salute e della Scienza di Torino, Torino, Italy; <sup>r</sup>Onco-Ematologia Ospedale Pagandi, Salerno, Italy; <sup>s</sup>Medicine I and Hematology, San Paolo Hospital, Savona, Italy; <sup>t</sup>Affiliate Clinic of Hematology Ospedali Riuniti, Ancona, Italy; <sup>u</sup>S.C. Onco-Ematologia, A.O.S. Maria di Terni, Terni, Italy; <sup>v</sup>Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRST, IRCCS, Meldola, Italy; <sup>w</sup>Hematology Unit, ASL Napoli 1 Centro, Naples, Italy; <sup>x</sup>Department of Hematology, Lymphoma Unit, Spirito Santo Hospital, Pescara, Italy

Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Lenalidomide • Mantle cell lymphoma • Relapsed • Refractory • Real life

## ABSTRACT

**Background.** Mantle cell lymphoma (MCL) has the worst prognosis of B-cell subtypes owing to its aggressive clinical disease course and incurability with standard chemo-immunotherapy. Options for relapsed MCL are limited, although several single agents have been studied. Lenalidomide is available in Italy for patients with MCL based on a local disposition of the Italian Drug Agency.

**Subjects, Materials, and Methods.** An observational retrospective study was conducted in 24 Italian hematology centers with the aim to improve information on effectiveness and safety of lenalidomide use in real practice.

**Results.** Seventy patients received lenalidomide for 21/28 days with a median of eight cycles. At the end of therapy, there were 22 complete responses (31.4%), 11 partial responses, 6 stable diseases, and 31 progressions, with an overall response rate of

47.1%. Eighteen patients (22.9%) received lenalidomide in combination with either dexamethasone ( $n = 13$ ) or rituximab ( $n = 5$ ). Median overall survival (OS) was reached at 33 months and median disease-free survival (DFS) at 20 months: 14/22 patients are in continuous complete response with a median of 26 months. Patients who received lenalidomide alone were compared with patients who received lenalidomide in combination: OS and DFS did not differ. Progression-free survivals are significantly different: at 56 months, 36% in the combination group versus 13% in patients who received lenalidomide alone. Toxicities were manageable, even if 17 of them led to an early drug discontinuation.

**Conclusion.** Lenalidomide therapy for relapsed MCL patients is effective and tolerable even in a real-life context. *The Oncologist* 2018;23:1033–1038

**Implication for Practice:** Several factors influence treatment choice in relapsed/refractory mantle cell lymphoma (rrMCL), and the therapeutic scenario is continuously evolving. In fact, rrMCL became the first lymphoma for which four novel agents have been approved: temsirolimus, lenalidomide, ibrutinib, and bortezomib. The rrMCL therapeutic algorithm is not so well established because data in the everyday clinical practice are still poor. Lenalidomide for rrMCL patients is effective and tolerable even in a real-life context.

Correspondence: Pier Luigi Zinzani, M.D., Ph.D., Institute of Hematology "L. e A. Seràgnoli," University of Bologna, Via Massarenti, 9 – 40138 Bologna, Italy. Telephone: 39 051 214 3680; e-mail: pierluigi.zinzani@unibo.it Received October 23, 2017; accepted for publication March 6, 2018; published Online First on April 19, 2018. <http://dx.doi.org/10.1634/theoncologist.2017-0597>

## INTRODUCTION

Mantle cell lymphoma (MCL) is an uncommon type of non-Hodgkin lymphoma (NHL) comprising <10% of all newly diagnosed patients. Nevertheless, there has been a significant increase in the MCL incidence over the past 2 decades, mostly among older patients [1]. Classified as an aggressive NHL subtype, MCL has the worst prognosis among the B-cell subtypes due to its aggressive clinical disease course and its inability to be treated with standard chemotherapy.

Although MCL is a rare subtype of NHL, proactive research efforts fueled by challenges in the management of this disease have led to an increase in median overall survival (OS) of 2.5 years in the last 20 years. This OS improvement is mostly due to the use of dose-intensive strategies, particularly cytarabine-containing regimens (with or without high-dose therapy [HDT] followed by autologous stem cell transplantation [ASCT] consolidation), which are associated with deeper remission (and higher molecular complete response [CR] rate), as well as due to better salvage therapies [2, 3]. MCL became the first lymphoma for which four novel agents have been approved in the relapsed/refractory setting: temsirolimus (only in Europe), lenalidomide, ibrutinib, and bortezomib (the last agent is approved only in the U.S., both in relapsed/refractory [rr] disease and in first-line combination therapy) [4–9]. Study findings confirm continuous improvement in the outcomes of MCL patients over the past decades, but they also highlight the challenge of improving long-term outcomes, particularly among older patients [1].

In routine practice (i.e., outside a clinical trial setting), the outcome of rrMCL remains overall unchanged both with standard immunochemotherapy and even after HDT-ASCT. In fact, most patients still relapse and frequently develop chemoresistance. The persistent lack of consensus for the treatment of rrMCL and the different geographical approval of the abovementioned single agents explain the rather impressive variability in the management of these patients across countries [9, 10].

Lenalidomide, an immunomodulator drug with direct anti-neoplastic effects, was recently approved in the U.S. for rrMCL. Several phase II studies on lenalidomide have provided substantial overall response rate (ORR; 28%–53%) with durable activity in heavily pretreated patients [3, 5, 6, 9, 11]. In the phase II, multicenter, open-label pivotal trial in the European Union (MCL-002-SPRINT), 254 patients with rrMCL were randomized 2:1 to lenalidomide monotherapy or investigator's choice (IC) monotherapy (rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine) [12]. At a median follow-up of 15.9 months, lenalidomide significantly improved progression-free survival (PFS) compared with IC (median 8.7 vs. 5.2 months,  $p = .004$ ). ORR was 40% (5% CR/CRu (unconfirmed CR)) for lenalidomide and 11% (0% CR/CRu) for IC. Median duration of response (DoR; 16.1 vs. 10.4 months) and OS (27.9 vs. 21.2 months) also encouraged the use of lenalidomide. The most common grade 3 or 4 adverse events (AEs) were neutropenia (44% vs. 34%) without increased risk of infection, thrombocytopenia (18% vs. 28%), leukopenia (8% vs. 11%), and anemia (8% vs. 7%) in the lenalidomide and IC groups, respectively. Analysis of subgroups and regression analyses associated better PFS with lenalidomide than with IC therapy, irrespective of prior

treatment history [13]. In terms of combinations, lenalidomide plus chemotherapy or targeted agents has also been investigated in patients with rrNHL [14–17]. The addition of lenalidomide has resulted in favorable response rates and improved outcomes. In a phase II study of patients with relapsed/refractory indolent NHL, treatment with lenalidomide plus rituximab was associated with an ORR of 78% among 18 evaluable patients, including a 33% CR rate. Lenalidomide plus rituximab has also been investigated in patients with rrMCL. In the phase II portion of a phase I/II study, ORR was 57% among the 44 patients, and 36% achieved a CR [18]. A previous large report on patients who underwent lenalidomide treatment through named patient program (NPP) showed an ORR of 45.5% in the MCL subset with a median DoR of 8.8 months [19, 20].

Lenalidomide is available in Italy for patients with rrMCL (without any other therapeutic options) since May 2011, based on a local disposition of the Italian Drug Agency (AIFA) issued according to a national law (Law 648/96: “medicinal products that are provided free of charge on the National Health Service”). An observational retrospective study was conducted in 24 Italian hematologic centers with the aim to improve information on effectiveness and safety of lenalidomide when given in everyday clinical practice.

## SUBJECTS, MATERIALS, AND METHODS

### Study Design

This was a multicenter, retrospective, observational study aimed at collecting data on the effectiveness and the safety of lenalidomide requested pursuant to Italian law 94/1998 in rrMCL patients. All patients who underwent lenalidomide therapy from 2011 to 2013 were deemed eligible for the study. A total of 24 Italian centers that had made at least one request for a supply of lenalidomide for nominal use were invited to participate in the study. Institutional Review Boards/Independent Ethics Committees approved the study at each institute in accordance with local rules and regulations (the Lenamant Study, recorded in the AIFA Observational Studies Registry). Participants gave their written informed consent in accordance with the Declaration of Helsinki.

### Objectives and Endpoints

The primary study objective was the effectiveness of lenalidomide in rrMCL patients, measured as ORR (defined as CR + partial response [PR] rate). The secondary objectives were survival of patients (measured as PFS, OS, disease-free survival [DFS], and DoR) and safety of lenalidomide (measured by recording any AE and/or hospitalization that occurred during or immediately after treatment with the study drug).

### Effectiveness Assessments and Statistical Methods

OS was calculated from start of treatment to the date of death due to any cause and was censored at the last date the patient was known to be alive. DFS was calculated for CR patients from first documentation of response to the date of relapse or death due to lymphoma or acute toxicity of treatment, whereas PFS was calculated for all patients from the start of treatment to relapse or death due to any cause. Duration of response was

**Table 1.** Patient demographics and characteristics at baseline ( $n = 70$ )

Characteristics	Whole population, $n = 70$ , $n$ (%)	Patients in continuous complete remission, $n = 14$ , $n$ (%)
Median age, years (range)	67 (45–85)	63 (45–79)
<65 years	57 (81.4)	8 (57.1)
≥65 years	13 (18.6)	6 (42.9)
Male	50 (71.4)	8 (57.1)
Stage		
I/II	14 (20.0)	4 (28.6)
III	5 (7.1)	1 (7.1)
IV	51 (72.9)	9 (62.3)
ECOG performance status		
0/1	47 (67.1)	12 (85.7)
2	17 (24.3)	2 (14.3)
3	2 (2.9)	—
4	1 (1.4)	—
B symptoms	10 (14.3)	1 (7.1)
Refractory to most recent therapy	32 (45.7)	4 (37.7)
Refractory to first-line therapy	16 (22.8)	9 (62.3)
Median number of previous therapies (range)	2.5 (1–10)	2 (1–5)
Prior autologous stem cell transplant	36 (51.4)	8 (57.1)
Lenalidomide single agents	52 (74.3)	8 (57.1)
Lenalidomide in combination	18 (25.7)	6 (42.9)

Abbreviations: —, no data; ECOG, Eastern Cooperative Oncology Group.

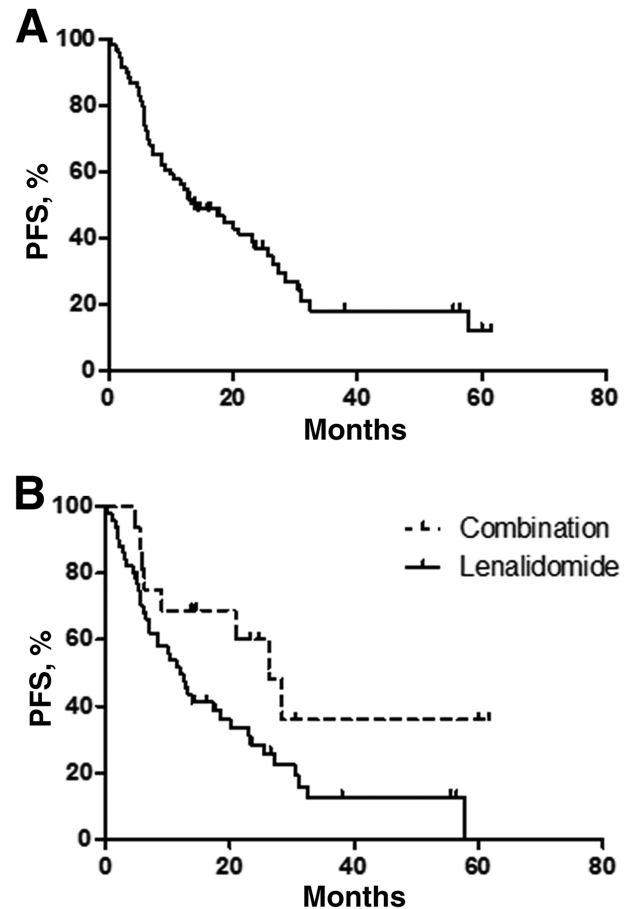
calculated in CR or PR patients from the first documentation of response to time of relapse or progression [21]. The determination of tumor response was based on the revised response criteria for malignant lymphoma [21]. Definition of older patients refers to the ones aged  $\geq 65$  years at lenalidomide start. Safety and tolerability were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Both patients treated with lenalidomide alone and with lenalidomide in combination with another drug (dexamethasone or rituximab) were analyzed.

Demographics and patients' characteristics as well as AEs were summarized by descriptive statistics. Survival functions were estimated by using the Kaplan-Meier method and were compared using log-rank test. Statistical analyses were performed with Stata 11 (StataCorp LLC, College Station, TX), and  $p$  values were set at .05.

## RESULTS

### Patient Demographics

The total population included 70 patients: 52 were treated with lenalidomide alone and 18 had combined therapy (13 received lenalidomide plus dexamethasone and 5 lenalidomide and rituximab, respectively). Table 1 summarizes the characteristics of all 70 evaluable patients. Median age at lenalidomide



**Figure 1.** Progression-free survival of the whole study population (A) and according to the monotherapy versus combined treatment subsets (B).

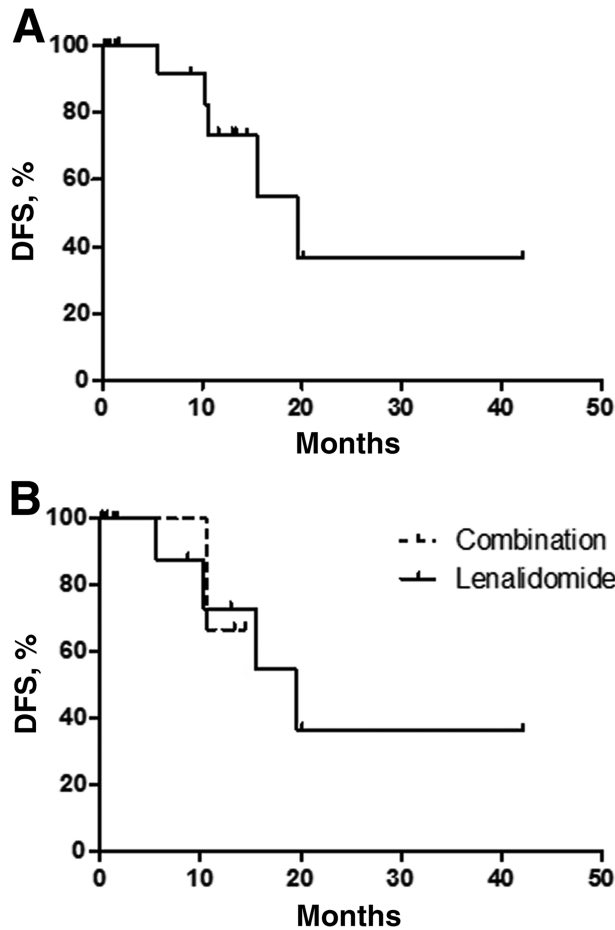
Abbreviation: PFS, progression-free survival.

was 67 (range 45–85) years; in particular, 57 patients (81.4%) were aged  $\geq 65$  years at treatment start. The majority of the population (71.4%) were male. The median number of prior treatment regimens was 2.5 (range 1–10); 32 (45.7%) patients were refractory to the last treatment, and 16 (22.8%) patients were primary refractory.

### Effectiveness

Overall, 688 cycles were completed for the 70 patients, with 11 (15.7%) patients receiving a 10 mg/day dose, 16 (22.8%) patients receiving a 15 mg/day dose, and 43 (61.5%) patients receiving a 25 mg/day dose. Of the 27 patients who received lenalidomide at the dose of 10 or 15 mg, 4 had combination therapy. The initial dose depended on physician choice based on hematologic parameters at baseline and known drug toxicities.

With a median of 8 cycles (range 1–55) and independently by the drug dose, the ORR was 47.1%. A total of 22 (31.4%) patients achieved a CR, 11 (15.7%) obtained a PR, 6 had SD, and 31 showed PD. Among the 52 patients treated with monotherapy with lenalidomide, 14 (26.9%) achieved a CR and 5 (9.6%) obtained a PR, leading to an ORR of 36.5%. On the other hand, in the combined therapy subset (18 patients), we observed an ORR of 77.7% with eight (44.4%) CRs and six (33.3%) PRs; more specifically, the two different combinations (namely lenalidomide plus dexamethasone and lenalidomide plus rituximab) did not show any statistically significant



**Figure 2.** Disease-free survival of the whole study population (A) and according to the monotherapy versus combined treatment subsets (B).

Abbreviation: DFS, disease-free survival.

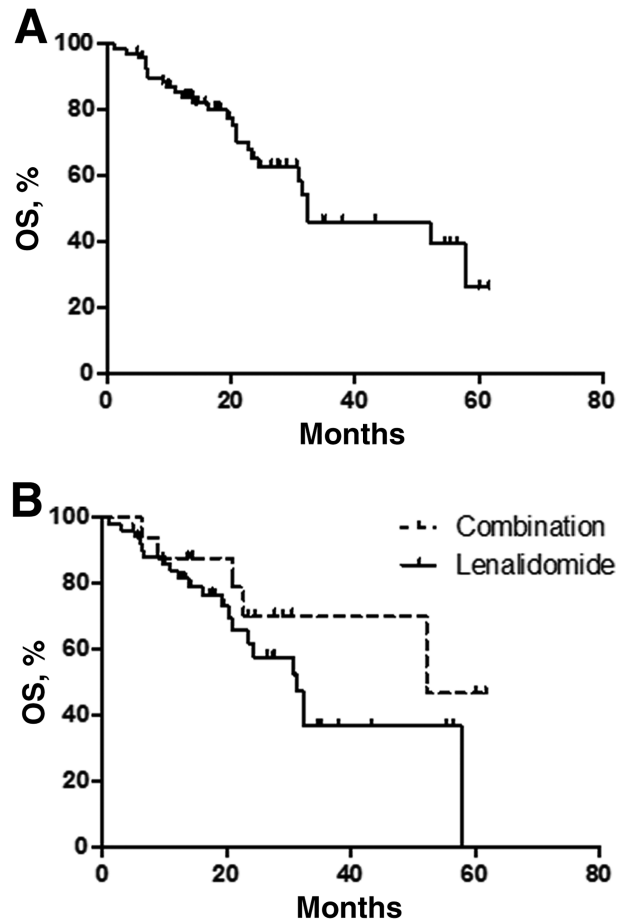
difference in terms of ORR and CR rates. The ORR was higher in patients who responded to last previous therapy (52.6%) compared with those who were refractory (34.4%). Progressive disease was found in 56.3% of refractory patients compared with 39.5% of responding patients. There was no significant difference in ORR between younger (38.5%) and older (45.6%) patients.

Median DoR was 17.8 months and 19.4 months in patients treated with monotherapy and combined therapy, respectively.

### Outcome

At the latest available follow-up, 14 patients were in continuous CR with a median follow-up of 26 months (range 13.8–62.7 months); specifically, 6 underwent combined therapy and 8 received lenalidomide as single agent. Table 1 summarizes the clinical characteristics of these patients.

Median PFS was 13.8 months in all patients (Fig. 1A), and, according to the monotherapy versus combined treatment subsets, the median PFS was 26.3 months versus 12.1 months, respectively (Fig. 1B,  $p < .001$ ). Median DFS was 19.6 months in all patients (Figure 2A), and, according to the monotherapy versus combined treatment subsets, the median DFS was 19.6 months versus not reached, respectively (Fig. 2B, no significant difference). Median OS was 32.5 months in all study population (Fig. 3A), and, according to the single-agent versus combined



**Figure 3.** Overall survival of the whole study population (A) and according to the monotherapy versus combined treatment subsets (B).

Abbreviation: OS, overall survival.

treatment subsets, the median OS was 31.4 versus 52.2 months, respectively (Fig. 3B, no significant difference). Globally, 26 patients died. No patient from this population was lost to follow-up. A total of 34 patients (namely 8 who received lenalidomide in combination with another drug and 26 who received lenalidomide alone) underwent further treatment after lenalidomide failure with a median time to the next treatment of 3.4 months.

### Safety

AEs were reported in 42 patients (60%), and SAEs were reported in 9 patients (12.8%). Observed AEs in patients included neutropenia ( $n = 25$ ), thrombocytopenia ( $n = 6$ ), anemia ( $n = 6$ ), and gastrointestinal toxicity ( $n = 4$ ), which are consistent with other published reports. Serious AEs included one lung carcinoma, one myelodysplastic syndrome, two myocardial infarctions judged not related to drug, and one infective episode and four gastrointestinal toxicities probably related to lenalidomide. Besides progression of disease, other causes of early discontinuation were the abovementioned 9 SAEs and 8 recurrent grade 4 neutropenia, for a total of 17 cases.

### DISCUSSION

Lenalidomide, an immunomodulatory drug with direct antineoplastic effects, recently approved in the U.S. for rMCL as single



agent, provided in several studies substantial ORR (28%–53%) with durable activity (median DoR, 13.7–16.6 months) in heavily pretreated patients, including those failing bortezomib [5] and ibrutinib [22, 23]. Recent results from MCL-002, a randomized phase II study of rrMCL patients, demonstrated a better median PFS with lenalidomide than with investigator's choice [12, 13].

Lenalidomide plus rituximab has demonstrated activity in several phase II studies across various NHL subpopulations in the relapsed/refractory setting. For example, this combination regimen resulted in a 74% ORR (44% CR rate and 12.4 months median PFS) in patients with indolent lymphoma and a 33% ORR (22% CR rate, 3.7 months median PFS, and 10.7 months median OS) in patients with aggressive lymphoma [14–16].

Based on established efficacy in multiple myeloma, lenalidomide in combination with the anti-inflammatory agent dexamethasone was investigated in patients with heavily pretreated rrMCL, obtaining an ORR of 52% [17, 18]. Besides the clinical trials context, a retrospective report on a large NPP in Italy was also published, but several types of lymphoma were included: ORR was 42.2% in the whole population and 45.5% in the rrMCL subset ( $n = 33$ ) [20].

Our retrospective analysis on 70 patients reported that ORR and CR rate were similar to those observed in clinical trials investigating similar MCL populations treated with lenalidomide as single agent or in combination with rituximab/dexamethasone. In fact, 26.9% of patients treated in monotherapy with lenalidomide achieved a CR and 9.6% obtained a PR with an ORR of 36.5%. In the combined therapy subset, the ORR was 77.7% with a 44.4% CR rate. In addition, similar effectiveness was found among younger and older patients.

The present study, which represents the largest report on lenalidomide in rrMCL patients in the standard daily clinical practice outside a trial setting, demonstrates that lenalidomide is a feasible treatment option for patients with rrMCL, even in real life. Separate analysis results for patients treated with lenalidomide alone or in combination (with dexamethasone or rituximab) give a more precise idea on the activity and safety of the drug to physicians who plan to use it, limiting bias in data interpretation.

Lenalidomide was used in a wide spectrum of patients with varied underlying diseases and a broad range of concomitant

medications; thus, the present data have the best picture of the drug's behavior in routine use.

## CONCLUSION

Despite the known potential bias of all observational studies, the present report on the real-life experience provides an important contribution to medical knowledge. Treatment with lenalidomide is effective and tolerable in everyday clinical practice, with superimposable results to those obtained in clinical trials, and it must be considered in the therapeutic algorithm of rrMCL as a targeted approach [3, 10].

## ACKNOWLEDGMENTS

We thank Celgene International Srl for unconditional support.

## AUTHOR CONTRIBUTIONS

**Conception/design:** Vittorio Stefoni, Lisa Argnani, Pier Luigi Zinzani

**Provision of study material or patients:** Vittorio Stefoni, Cinzia Pellegrini, Alessandro Broccoli, Luca Baldini, Monica Tani, Emanuele Cencini, Amalia Figuera, Michela Ansuinelli, Elisa Bernocco, Maria Cantonetti, Maria Christina Cox, Filippo Ballerini, Chiara Rusconi, Carlo Visco, Luca Arcaini, Angelo Fama, Roberto Marasca, Stefano Volpetti, Alessia Castellino, Catello Califano, Marina Cavaliere, Guido Gini, Anna Marina Liberati, Gerardo Musuraca, Anna Lucania, Giuseppina Ricciuti, Pier Luigi Zinzani

**Collection and/or assembly of data:** Vittorio Stefoni, Cinzia Pellegrini, Alessandro Broccoli, Luca Baldini, Monica Tani, Emanuele Cencini, Amalia Figuera, Michela Ansuinelli, Elisa Bernocco, Maria Cantonetti, Maria Christina Cox, Filippo Ballerini, Chiara Rusconi, Carlo Visco, Luca Arcaini, Angelo Fama, Roberto Marasca, Stefano Volpetti, Alessia Castellino, Catello Califano, Marina Cavaliere, Guido Gini, Anna Marina Liberati, Gerardo Musuraca, Anna Lucania, Giuseppina Ricciuti, Lisa Argnani, Pier Luigi Zinzani

**Data analysis and interpretation:** Vittorio Stefoni, Lisa Argnani, Pier Luigi Zinzani

**Manuscript writing:** Vittorio Stefoni, Lisa Argnani, Pier Luigi Zinzani

**Final approval of manuscript:** Vittorio Stefoni, Cinzia Pellegrini, Alessandro Broccoli, Luca Baldini, Monica Tani, Emanuele Cencini, Amalia Figuera, Michela Ansuinelli, Elisa Bernocco, Maria Cantonetti, Maria Christina Cox, Filippo Ballerini, Chiara Rusconi, Carlo Visco, Luca Arcaini, Angelo Fama, Roberto Marasca, Stefano Volpetti, Alessia Castellino, Catello Califano, Marina Cavaliere, Guido Gini, Anna Marina Liberati, Gerardo Musuraca, Anna Lucania, Giuseppina Ricciuti, Lisa Argnani, Pier Luigi Zinzani

## DISCLOSURES

**Luca Arcaini:** Celgene, Roche, Bayer, Sandoz (C/A), Gilead (RF), Roche, Celgene, Gilead, Sandoz (SAB). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

## REFERENCES

- Epperla N, Hamadani M, Fenske TS et al. Incidence and survival trends in mantle cell lymphoma. *Br J Haematol* 2017 [Epub ahead of print].
- Abrahamsson A, Albertsson-Lindblad A, Brown PN et al. Real world data on primary treatment for mantle cell lymphoma: A Nordic Lymphoma Group observational study. *Blood* 2014;124:1288–1295.
- Dreyling M, Campo E, Hermine O et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28(suppl 4):iv62–iv71.
- Hess G, Herbrecht R, Romaguera J et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2009;27:3822–3829.
- Goy A, Sinha R, Williams ME et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study. *J Clin Oncol* 2013;31:3688–3695.
- Zinzani PL, Vose JM, Czuczman MS et al. Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: Subset analysis of the NHL-003 study. *Ann Oncol* 2013;24:2892–2897.
- Wang ML, Rule S, Martin P et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507–516.
- Fisher RI, Bernstein SH, Kahl BS et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2006;24:4867–4874.
- Robak T, Huang H, Jin J et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med* 2015;372:944–953.
- The NCCN Clinical Practice Guidelines for non-Hodgkin lymphomas. Available at <https://www.nccn.org/about/nhl.pdf>. Accessed October 27, 2017.
- Habermann TM, Lossos IS, Justice G et al. Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma. *Br J Haematol* 2009;145:344–349.
- Trnny M, Lamy T, Walewski J et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): A phase 2, randomised, multicentre trial. *Lancet Oncol* 2016;17:319–331.

13. Trneny M, Lamy T, Walewski J et al. Impact of prior treatment on PFS for relapsed/refractory mantle cell lymphoma patients randomized to lenalidomide vs investigator's choice: A subgroup analysis of the phase II MCL-002 (SPRINT) study. *Haematologica* 2015;100:4.
14. Tuscano JM, Dutia M, Chee K et al. Lenalidomide plus rituximab can produce durable clinical responses in patients with relapsed or refractory, indolent non-Hodgkin lymphoma. *Br J Haematol* 2014;165:375–381.
15. Wang M, Fowler N, Wagner-Bartak N et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: A phase II clinical trial. *Leukemia* 2013;27:1902–1909.
16. Chong EA, Ahmadi T, Aquilino NA et al. Combination of lenalidomide and rituximab overcomes rituximab resistance in patients with indolent B-cell and mantle cell lymphomas. *Clin Cancer Res* 2015;21:1835–1842.
17. Ahmadi T, Chong EA, Gordon A et al. Combined lenalidomide, low-dose dexamethasone, and rituximab achieves durable responses in rituximab-resistant indolent and mantle cell lymphomas. *Cancer* 2014;120:222–228.
18. Zaja F, De Luca S, Vitolo U et al. Salvage treatment with lenalidomide and dexamethasone in relapsed/refractory mantle cell lymphoma: Clinical results and effects on microenvironment and neoangiogenic biomarkers. *Haematologica* 2012;97:416–422.
19. Zinzani PL, Rigacci L, Cox MC et al. Lenalidomide monotherapy in heavily pretreated patients with non-Hodgkin lymphoma: An Italian observational multicenter retrospective study in daily clinical practice. *Leuk Lymphoma* 2015;56:1671–1676.
20. Zinzani PL, Rigacci L, Cox MC et al. The efficacy of lenalidomide combination therapy in heavily pretreated non-Hodgkin lymphoma patients: An Italian observational, multicenter, retrospective study. *Leuk Lymphoma* 2017;58:226–229.
21. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579–586.
22. Wang M, Schuster SJ, Phillips T et al. Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004). *J Hematol Oncol* 2017;10:171.
23. Epperla N, Hamadani M, Cashen AF et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-A “real world” study. *Hematol Oncol* 2017;35:528–535.

#### For Further Reading:

Hun Ju Lee, Jorge E. Romaguera, Lei Feng et al. Phase II Study of Bortezomib in Combination with Cyclophosphamide and Rituximab for Relapsed or Refractory Mantle Cell Lymphoma. *The Oncologist* 2017;22:549-553.

#### Implications for Practice:

The combination of bortezomib with cyclophosphamide and rituximab represents an additional effective novel salvage regimen for mantle cell lymphoma. This combination adds to the growing list of treatment options available for patients with mantle cell lymphoma.