IELSG40/CLEO phase II trial of clarithromycin and lenalidomide in relapsed/refractory extranodal marginal zone lymphoma

Currently, there is not a single standard of care for patients with relapsed/refractory (R/R) marginal zone lymphoma (MZL), in whom avoiding overtreatment and superfluous toxicity is particularly important since they have an overall good prognosis.[1]

Lenalidomide as a single agent induced objective responses in roughly 60% of a series of 18 patients with either newly diagnosed or R/R extranodal MZL enrolled in a phase II trial at the University of Vienna.[2] Clarithromycin has clinical antineoplastic activity in MZL;[3,4] moreover, its addition to lenalidomide has been able to revert lenalidomide resistance in multiple myeloma patients.[5] Based on these data, the International Extranodal Lymphoma Study Group (IELSG) designed the IELSG40/CLEO phase II trial (NCT03031483/EudraCT2015-003168-35) to investigate efficacy and safety of a full oral combination of clarithromycin plus lenalidomide in patients with R/R extranodal MZL. Patients received clarithromycin 500 mg *b.i.d.* on days 1-28 and lenalidomide 20 mg once daily on days 1-21 of repeated 28-day cycles. All patients but one received concomitant deep venous thrombosis prophylaxis. The dose of lenalidomide was reduced to 15 mg/day (and, if needed, to 10 mg/day in subsequent cycles) after any adverse event of grade >2 according to NCI-CTCAE version 4.03. No dose reduction was planned for clarithromycin. After the first three cycles, patients with stable disease or a better response received three further cycles. After the sixth, and again after the ninth cycle, treatment was discontinued in patients with progressive disease or complete response (CR), while patients with a partial response (PR) or stable disease received three further cycles, up to a maximum of 12.

The primary endpoint was the overall response rate, defined as the proportion of patients with a CR or PR according to the revised response criteria for malignant lymphoma.[6] Patients with gastric lymphoma were evaluated endoscopically and histologically using the GELA scoring system.[7] The hypothesis for sample size calculation was that clarithromycin can overcome resistance to lenalidomide leading to a clinically relevant 15% improvement of the overall response rate (from the 60% expected with lenalidomide alone).[2] The trial was planned, with 5% significance and 80% power, according to the Simon minimax design,[8] with the study treatment being considered of no interest if fewer than 19 of the first 30 patients achieved a PR or CR. Conversely, the treatment was considered active in the case of at least 44 responses in a total of 62 patients. Enrollment was not halted while waiting for response assessment in the first 30 patients. Secondary endpoints included safety, progression-free survival (calculated from the start of treatment to relapse/progression or death of any cause), overall survival (calculated from the start of treatment to death of any cause) and duration of response (calculated from achievement of partial or complete response to relapse/progression).[6]

Patients were enrolled in ten institutions, between March 2017 and October 2019. Patients older than 18 years with extranodal MZL refractory to or following ≥1 relapses after radiotherapy and/or chemotherapy and/or immunotherapy were eligible. Inclusion criteria comprised the presence of measurable disease or non-measurable lesions for which response was evaluable by non-imaging means (e.g., gastric or bone marrow infiltrations). Other eligibility criteria included Eastern Cooperative Oncology Group performance status ≤2, and adequate organ function. Exclusion criteria comprised a lymphoma histology other than extranodal MZL and clinically significant comorbidities. Ethics committees of the participating centers approved the study and all patients provided written informed consent. Forty-four patients were enrolled. One of them did not receive the study treatment after a revised diagnosis of diffuse large B-cell lymphoma. Enrollment was terminated after the first-step analysis in the first 30 patients showed an overall response rate of 44%, which did not meet the predefined threshold, while the patients already recruited continued the study treatment.

Table 1 summarizes the characteristics of the 43 eligible patients; one-third of them had a high-risk MALT-IPI score[9] and 53% had stage IV disease. Forty-one patients (95%) had received one to six lines of previous systemic therapy and two had previously received only radiotherapy. The enrollment of patients with multiple relapses (47% had received ≥2 prior therapies) may explain the disease localizations at anatomic sites rarely involved at presentation.

At a median follow-up of 23.5 months (interquartile range, 9.4-37 months), the best response was a CR in six patients, PR in 13 and stable disease in 14 (Table 2). Five patients had progressive disease (3 with gastric, 1 with lung and 1 with salivary gland lymphoma). Response was not evaluable in five patients: three because of consent with-

drawal and two because of early treatment discontinuation after serious adverse events (fever and pulmonary thromboembolism). In the intent-to-treat population (n=43), the overall response rate was 44% (95% confidence interval [95% CI]: 29-60%) with a CR rate of 14% (95% CI: 5-28%). The overall response rate and CR rate were 50% (95% CI: 33-67%) and 16% (95% CI: 6-31%), respectively, in the subset of 38 evaluable patients, of whom 29 were assessed by computed tomography scan, and nine (with localized gastric involvement) by repeat endoscopic biopsy only.

Table 1. Characteristics of the patients (N=43) at study entry.

Clinical features	
Age, years, median (range)	69 (43-87)
Sex N (%) Male Female	 24 (56) 19 (44)
ECOG performance status, N (%) 0 1	 39 (91) 4 (9)
Anemia, N (%)	5 (12)
Elevated serum LDH, N (%)	8 (19)
Stage, N (%) I-II III-IV	 19 (44) 24 (56)
MALT-IPI prognostic index, N (%) Low risk Intermediate risk High risk	 6 (14) 23 (53) 14 (33)
N of prior systemic treatments, N (%) 1 2 3 6	 23 (54) 10 (23) 7 (16) 1 (2)
Type of previous systemic treatments, N (%) Anti-CD20 antibody in any previous line of therapy Anti-CD20 antibody in the last line before the present study Alkylating agents Lenalidomide Clarithromycin	 39 (91) 28 (65) 18 (42) 5 (12) 7 (16)
Prior radiotherapy only, N (%)	2 (5)
Main site of relapsing/refractory disease, N (%) Stomach* Ocular adnexa** Lung Salivary glands Liver Skin Subcutaneous tissue Breast Kidneys Bone Muscle	 11 (26) 8 (19) 6 (14) 4 (9) 4 (9) 3 (7) 2 (5) 2 (5) 1 (2) 1 (2) 1 (2)

*All with no evidence of *H. pylori* infection at study entry. **All either C. *psittaci*-negative at diagnosis or with successful *Chlamydia* eradication prior to study entry. ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MALT-IPI: Mucosa-associated lymphoma tissue-International Prognostic Index.

Twenty-one (49%) patients completed the entire protocol-planned treatment program; six of them achieved a CR, and eight had a PR (Table 2). Six of the eight patients previously exposed to the study drugs were assessable for response; two had progressive disease, two had stable disease and two had a PR. Notably, the response quality improved over time: of 11 patients with a PR at 3 months, three achieved a CR at 1 year; of 20 patients with stable disease at 3 months, one achieved a CR and three a PR at 1 year. Figure 1A depicts the individual patients' best response in radiologically measurable lesions. The median duration of resposne was not reached (Figure 1B) and the 2-year continuous remission rate in the 19 patients achieving a CR or PR was 71% (95% CI: 44-87%). Response rates by anatomic site are summarized in *Online Supplementary Table S1*.

In the intention-to-treat cohort, the median progression-free survival was 40 months with a 2-year progression-free survival rate of 53% (95% CI: 35-69%). Five deaths were reported. One patient in CR died from a second tumor (esophageal carcinoma, diagnosed 2 years after the completion of 12 cycles of treatment) and four due to lymphoma progression (with no biopsy performed to seek histological transformation). The median overall survival was not reached, with 86% (95% CI: 66-95%) of patients being alive at 2 years.

No toxic deaths were recorded. The most frequent adverse events of any grade were rash (35%), neutropenia (35%), asthenia (28%), and dysgeusia (28%). Diarrhea, vertigo, and arthralgia/myalgia were also frequently seen (21% each). Neutropenia was the commonest grade 3-4 adverse event, occurring in nine (21%) patients and lasting a median of 7 days; five patients were treated with granulocyte colony-stimulating factor. Thirteen serious adverse events were observed, with four reported as related to the study drug lenalidomide: basal cell carcinoma diagnosed 2 years after the study treatment completion, febrile neutropenia, fever, and pulmonary thromboembolism in the patient who was not given prophylaxis against deep vein thrombosis. No other severe thrombotic or hemorrhagic events were observed; only one case of superficial venous thrombosis (grade 1) and two episodes of bleeding (grade 2, gastric and retinal) were reported. The dose of lenalidomide was reduced to 15 mg/day in four patients, in one because of grade 3 hepatotoxicity and in three because of neutropenia.

Although our study was formally negative for its primary endpoint, the observed overall response rate in the efficacy population is comparable to response rates reported by the studies leading to US Food and Drug Administration approval of targeted therapies for R/R MZL, namely ibruti-

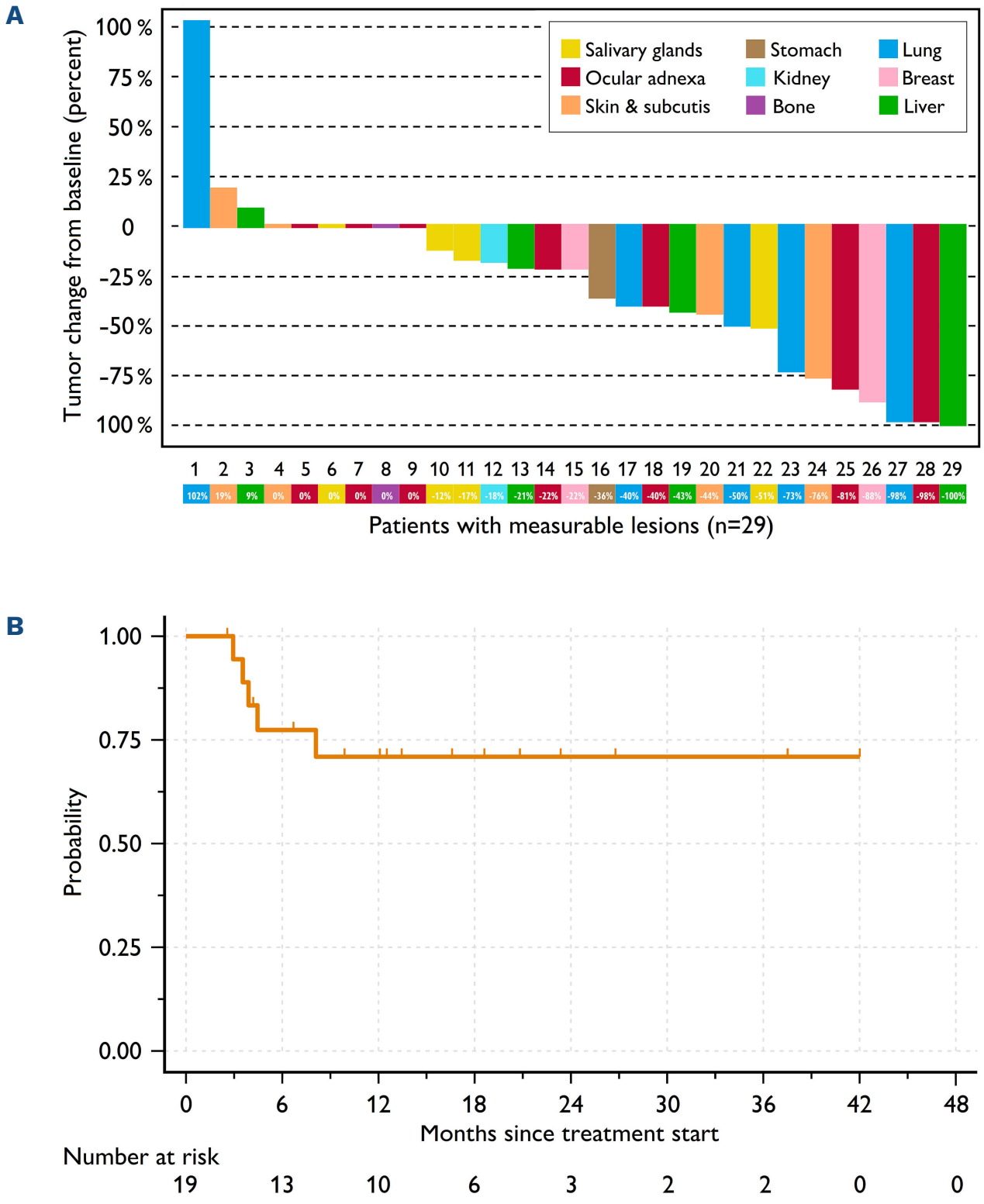

Figure 1. Response of patients with refractory/relapsed mantle zone lymphoma to treatment with the CLEO regimen. (A) Waterfall plot of percent change in radiologically measurable disease by primary anatomic site. The chart includes all the 28 evaluable patients with extra-gastric localizations and one patient who had gastric lymphoma with additional radiologically measurable disease (perigastric adenopathy). In the remaining nine evaluable patients, all with gastric lymphoma, response was assessed only by endoscopy and repeat biopsy, hence, they cannot be included in the graph. (B) Kaplan-Meier estimate of response duration in the 19 patients who achieved an objective response (complete or partial).

Table 2. Best response.

Response	ITT patient population (total 43 patients) N (%; 95% CI)	Evaluable patients (total 38 patients) N (%; 95% CI)	Treatment entirely completed (total 21 patients) N (%; 95% CI)
Overall response rate	19 (44; 29-60)	19 (50; 33-67)	14 (67; 43-85)
Complete response	6 (14; 5-28)	6 (16; 6-31)	6 (29; 11-52)
Partial response	13 (30; 17-46)	13 (34; 20-51)	8 (38; 18-62)
Stable disease	14 (33; 19-49)	14 (37; 22-54)	7 (33; 15-57)
Progressive disease	5 (12; 4-25)	5 (13, 4-28)	0
Not evaluable	5 (12; 4-25)	na	na

ITT: intent-to-treat; 95% CI: 95% confidence interval; na: not applicable.

nib,[10] copanlisib,[11] umbralisib[12] and zanubrutinib.[13] Our results also appear at least not inferior to those of a more recent phase II study evaluating the novel oral dual inhibitor of PI3K-δ/γ, duvelisib.[14] Moreover, the duration of response in our study (71% at 2 years, median not reached) appears very promising in comparison with the one reported with ibrutinib (median, 28 months)[10] and copanlisib (median, 17 months).[11]

On the other hand, the efficacy of our clarithromycin-lenalidomide regimen appears similar to that observed with clarithromycin alone.[3,4] Moreover, the overall response rate seems lower than the one reported in the study of lenalidomide alone, which we used for the sample size calculation.[2] Since there are no reasonable grounds to assume that the combination is detrimental, the most likely explanation for these findings is the inclusion of a sizable number (15% to 60%) of untreated patients and the significantly higher proportion of stage I patients (over 70%) in the prior studies.[2-4] This may also explain a higher lymphoma-related mortality (9%) in the present study than in the prior ones.[2-4] However, it is worth noting that, despite a lower overall response rate, the duration of response and progression-free survival are not inferior to those observed in the trial that led to approval by the Food and Drug Administration of the lenalidomide-rituximab combination for previously treated patients with indolent lymphoma.[15]

Even if we cannot draw definitive conclusions, the explored lenalidomide-clarithromycin combination was feasible and moderately active, with a favorable safety profile and efficacy analogous to that reported for other approved oral drugs. Given the relatively limited therapeutic options for patients with extranodal MZL experiencing multiple relapses, the CLEO combination (clarithromycin and lenalidomide) remains a potential alternative, particularly for frail patients who, all the more in times of the pandemic of coronavirus disease 2019, may not be suitable for treatments that weaken the immune response.

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Contributions

AJMF, MR, and EZ designed the trial and wrote the study protocol. MCP, MS, BK, AJMF, MR and EZ analyzed the data and wrote the manuscript. ALG, LD, EDD, AT, DM, MM, AS, and CV registered and treated patients, provided experimental data, and critically reviewed the manuscript draft. EZ, MCP, FE, and LB accessed and verified the trial data. LB coordinated regulatory activities and collection, assembly, and management of the data. All authors approved the definitive version of the manuscript and its submission.

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Data-sharing statement

The clinical trial (NCT03031483/ EudraCT 2015-003168-35) protocol will be made available upon request.

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