LETTER TO THE EDITOR

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

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Authorship

Contribution: **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**, **CV** registered and treated patients, provided experimental data, provided critical review of 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.

Currently, there is no single standard of care for relapsed/refractory (R/R) marginal zone lymphoma (MZL) patients, in whom avoiding overtreatment and superfluous toxicity is particularly important since they have an overall good prognosis (1).
Lenalidomide as 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 2 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 (DVT) prophylaxis. Lenalidomide dose was reduced to 15 mg/day (and, if needed, to 10 mg/day in subsequent cycles) after any adverse event (AE) of grade >2 according to NCI-CTCAE version 4.03. No dose reduction was planned for clarithromycin. After the first 3 cycles, patients in stable disease (SD) or with better response received 3 further cycles. After the sixth, and again after the ninth cycle, treatment was discontinued in patients with progressive disease (PD) or complete response (CR), while patients with partial responses (PR) or SD received 3 further cycles, up to a maximum of 12.

Primary endpoint was the overall response rate (ORR), defined as the proportion of patients with 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 ORR (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), being the study treatment considered of no interest if less than 19 of the first 30 patients achieved PR or CR. Conversely, the treatment was considered active in 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 (PFS, calculated from treatment start to relapse/progression or death as a result of any cause), overall survival (OS, from treatment start to death as a result of any cause) and duration of response (DOR, from achievement of PR or CR to relapse/progression) (6).

Patients were enrolled in 10 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 where response was evaluable by non-imaging means (e.g., gastric or bone marrow infiltrations). Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and adequate organ function. Exclusion criteria comprised a lymphoma histology other than extranodal MZL and clinically

significant comorbidities. Ethic 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 DLBCL. Enrollment was terminated after the first-step analysis in the first 30 patients showed an ORR 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 high-risk MALT-IPI score (9) and 53% had stage IV disease. Forty-one patients (95%) received 1 to 6 lines of previous systemic therapy and 2 received only prior radiotherapy. The enrollment of patients with multiple relapses (47% 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 CR in 6 patients, PR in 13 and SD in 14 (Table 2). Five patients had PD (3 with gastric, 1 with lung and 1 with salivary gland lymphoma). Response was not evaluable in 5 patients: 3 because of consent withdrawal and 2 because of early treatment discontinuation after serious AEs (fever and pulmonary thromboembolism respectively). In the intent-to-treat (ITT) population (N=43), ORR was 44% (95% CI, 29-60%) with a CR rate of 14% (95% CI, 5-28%). ORR and CR rates were 50% (95% CI, 33-67%) and 16% (95% CI, 6-31%), respectively, in the subset of 38 evaluable patients, of whom, 29 had assessment by computed tomography scan, and 9 (with localized gastric involvement) by repeat endoscopic biopsy only.

Twenty-one (49%) patients completed the entire protocol-planned treatment program; 6 of them achieved a CR, and 8 had a PR (Table 2). Six of the 8 patients previously exposed to the study drugs were assessable for response, 2 had PD, 2 SD and 2 a PR. Notably, the response quality improved over time; of 11 patients with PR at 3 months, 3 achieved a CR at 1 year; of 20 patients with SD at 3 months, 1 achieved a CR and 3 a PR at 1 year. Figure 1A depicts the individual patient's best response in radiologically measurable lesions. The median DOR was not reached (Figure 1B) and the 2-year continuous remission rate in the 19 patients achieving CR or PR was 71% (95%CI, 44-87%). Response rates by anatomic site are summarized in the supplemental Table S1.

In the ITT cohort, median PFS was 40 months with a 2-year PFS 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 4 due to lymphoma progression (with no biopsy performed to seek histological transformation). Median OS was not reached; 86% (95%CI, 66-95%) of patients were alive at 2 years.

No toxic deaths were recorded. The most frequent AEs of any grade were rash (35%), neutropenia (35%), asthenia (28%), dysgeusia (28%). Diarrhea, vertigo, arthralgia/myalgia were also frequently seen (21% each). Neutropenia was the commonest grade 3-4 AE, occurring in 9 (21%) patients, with a median duration of 7 days; 5 patients had G-CSF treatment. Thirteen serious AEs were observed, 4 reported as related to the study drug lenalidomide: basal cell carcinoma diagnosed two

years after the study treatment completion, febrile neutropenia, fever, and pulmonary thromboembolism in the patient with no DVT prophylaxis. No other severe thrombotic or hemorrhagic events were observed; only 1 case of superficial venous thrombosis (grade 1) and 2 episodes of bleeding (grade 2, gastric and retinal) were reported. Four patients had lenalidomide dose reduction to 15 mg/day, 1 for grade 3 hepatotoxicity and 3 for neutropenia.

Although our study was formally negative for its primary endpoint, the observed ORR in the efficacy population is comparable to response rates reported by the studies leading to US Food and Drug Administration (FDA) approval of targeted therapies for R/R MZL, namely ibrutinib (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 Pl3K-δ/γ, duvelisib (14). Moreover, the DOR 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 ORR seems lower than the one reported in the study of lenalidomide alone, which we used for 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 sizeable number (15% to 60%) of untreated patients and the significantly higher proportion of stage I patients (over 70%) in the prior reports (2-4). This may also explain a lymphoma-related mortality (9%) higher in the present study than in the prior ones (2-4). However, it is worth noting that, despite a lower ORR, DOR and PFS are not inferior to those observed in the trial that led to FDA approval 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 extranodal MZL patients experiencing multiple relapses, the CLEO combination remains a potential alternative, particularly for frail patients who, all the more in times of the COVID19 pandemics, may not be suitable for treatments that weaken the immune response.

References

1. Zucca E, Arcaini L, Buske C, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up□. Ann Oncol. 2020;31(1):17-29.

2. Kiesewetter B, Troch M, Dolak W, et al. A phase II study of lenalidomide in patients with extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT lymphoma). Haematologica. 2013;98(3):353-356.

3. Ferreri AJM, Cecchetti C, Kiesewetter B, et al. Clarithromycin as a "repurposing drug" against MALT lymphoma. Br J Haematol. 2018;182(6):913-915.

4. Pokorny A, Kiesewetter B, Raderer M. Experience with clarithromycin as antineoplastic therapy for extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma) outside of clinical trials: Real-world data from the University of Vienna. Hematol Oncol. 2020;38(3):409-411.

5. Ghosh N, Tucker N, Zahurak M, Wozney J, Borrello I, Huff CA. Clarithromycin overcomes resistance to lenalidomide and dexamethasone in multiple myeloma. Am J Hematol. 2014;89(8):E116-120.

6. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-586.

7. Copie-Bergman C, Wotherspoon AC, Capella C, et al. Gela histological scoring system for post-treatment biopsies of patients with gastric MALT lymphoma is feasible and reliable in routine practice. Br J Haematol. 2013;160(1):47-52.

8. Shan G, Zhang H, Jiang T. Minimax and admissible adaptive two-stage designs in phase II clinical trials. BMC Med Res Methodol. 2016;16:90.

9. Thieblemont C, Cascione L, Conconi A, et al. A MALT lymphoma prognostic index. Blood. 2017;130(12):1409-1417.

10. Noy A, de Vos S, Coleman M, Martin P, et al. Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis. Blood Adv. 2020;4(22):5773-5784.

11. Panayiotidis P, Follows GA, Mollica L, et al. Efficacy and safety of copanlisib in patients with relapsed or refractory marginal zone lymphoma. Blood Adv. 2021;5(3):823-828.

12. Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a Dual PI3Kδ/CK1ε Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2021;39(15):1609-1618.

13. Opat S, Tedeschi A, Linton K, et al. The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Clin Cancer Res. 2021;27(23):6323-6332.

14. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma. J Clin Oncol. 2019;37(11):912-922.

15. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199.

Table 1. Patient characteristics at study entry (N=43)

Clinical features	**N**	**%**
Median age	69 years (range, 43-87)	
Sex		
- Male	24	56
- Female	19	44
Performance status		
- ECOG0	39	91
- ECOG1	4	9
Anemia	5	12
Elevated serum LDH	8	19
Stage		
- I-II	19	44
- III-IV	24	56
MALT-IPI		
- Low risk	6	14
- Intermediate risk	23	53
- High risk	14	33
Number of prior systemic treatments		
- 1	23	54
- 2	10	23
- 3	7	16
- 6	1	2
Type of previous systemic treatments		
- Anti-CD20 antibody in any previous line of therapy	39	91
- Anti-CD20 antibody in the last line before the present study	28	65
- Alkylating agents	18	42
- Lenalidomide	5	12
- Clarithromycin	7	16
Prior radiotherapy only	2	5
Main site of relapsing/refractory disease		
- Stomach*	11	26
- Ocular adnexa**	8	19
- Lung	6	14
- Salivary glands	4	9
- Liver	4	9
- Skin	3	7
- Subcutaneous tissue	2	5
- Breast	2	5
- Kidneys	1	2
- Bone	1	2
- Muscle	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.

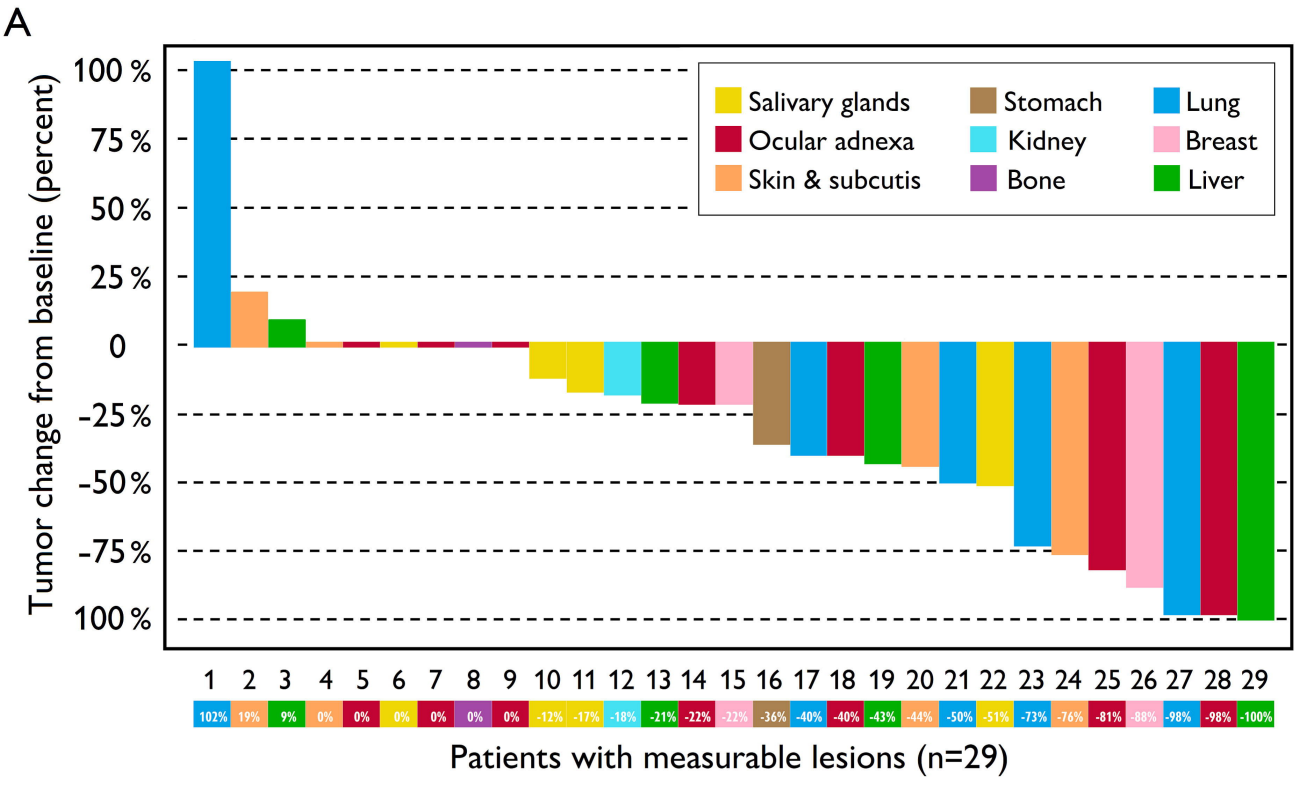
Table 2. Best response

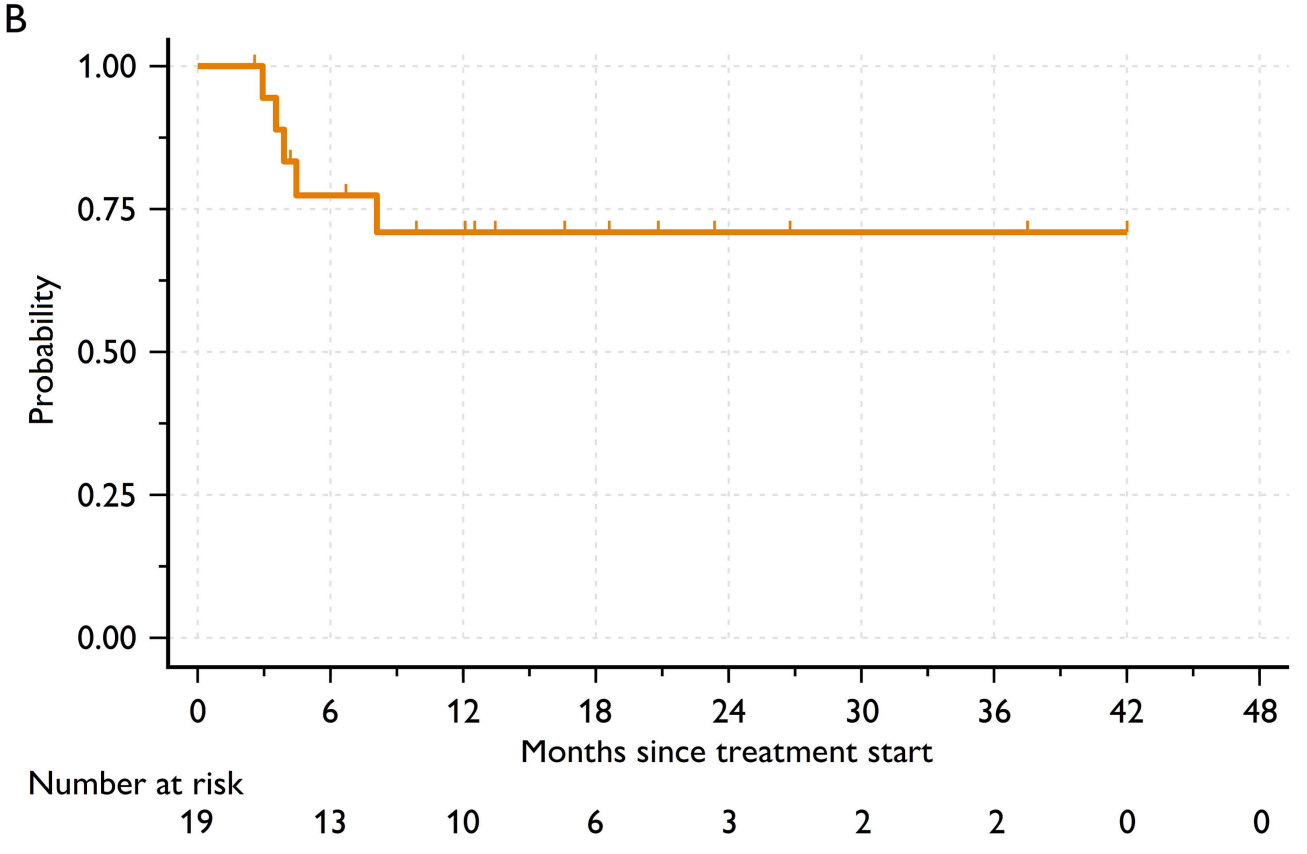
Response	**ITT patient population** *N (% ; 95%CI)*	**Evaluable patients** *N (%; 95%CI)*	**Treatment entirely completed** *N (%; 95%CI)*
Overall remission rate	19 (44%; 29-60%)	19 (50%; 33-67%)	14 (67%; 43-85%)
Complete remission	6 (14%; 5-28%)	6 (16%; 6-31%)	6 (29%; 11-52%%)
Partial remission	13 (30%; 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%)	n.a.	n.a.
Total	*43 (100%)*	*38 (100%)*	*21 (100%)*

ITT, intent-to-treat; n.a., not applicable.

Figure legend:

Figure 1. Response of R/R MZL patients to the 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 9 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 (CR or PR).


A
Tumor change from baseline (percent)
100 %
75 %
50 %
25 %
0
-25 %
-50 %
-75 %
100 %
Salivary glands
Ocular adnexa
Skin & subcutis
Stomach
Kidney
Bone
Lung
Breast
Liver
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
102% 19% 9% 0% 0% 0% 0% 0% 0% -12% -17% -18% -21% -22% -22% -36% -40% -40% -43% -44% -50% -51% -73% -76% -81% -88% -98% -98% -100%
Patients with measurable lesions (n=29)


B
Probability
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48
Months since treatment start
Number at risk
19 13 10 6 3 2 2 0 0

Supplementary data

Table S1: Response by anatomic site of disease

Anatomic Site	**CR** *N*	**PR** *N*	**SD** *N*	**PD** N	**NE** *N*	**ORR** *N (%; 95%CI)*[#]
Stomach	1	5	1	3	1	6 (54.5%; 24-83%)
Ocular adnexa	0	4	3	0	1	4 (50%; 16-84%)
Lung	2	2	0	1	1	4 (67%; 22-96%)
Salivary glands	0	0	3	1	0	0 (0%; 0-60%)*
Liver	1	0	3	0	0	1 (25%; 0.6-81%)
Skin	0	1	1	0	1	1 (33%; 0.8-91%)
Subcutaneous tissue	1	0	0	0	1	1 (50%; 1.25-99%)
Breast	1	0	1	0	0	1 (50%; 1.25-99%)
Kidney	0	1	0	0	0	1 (100%; 2.5-100%)*
Bone	0	0	1	0	0	0 (0%; 0-97.5%)*
Muscle	0	0	1	0	0	0 (0%; 0-97.5%)*

CR, complete remission; PR, partial remission, SD, stable disease; PD, progression of disease; NE not evaluable; ORR, overall response rate.
[#] Percentage and 95%CI refer to the intent-to-treat population.
* One-sided, 97.5% CI.