Second-line rituximab, lenalidomide, and bendamustine in mantle cell lymphoma: a phase II clinical trial of the Fondazione Italiana Linfomi

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SUPPLEMENTARY APPENDIX

Additional trial inclusion and exclusion criteria

Adult patients who met World Health Organization criteria for MCL[1] were eligible for inclusion if they had: an Eastern Cooperative Oncology Group performance status of ≤2; at least one site of measurable baseline nodal disease of ≥2.0 cm in the longest transverse diameter, as determined by computed tomography (CT) scan; adequate cardiac, hepatic, and renal function, and laboratory test results (absolute neutrophil count >1.5 x 10^9/L; platelet count >75 x 10^9/L; conjugated bilirubin, alkaline phosphatase, and transaminases ≤2 x upper limit of normal; calculated creatinine clearance ≥30 mL/min); and no prior malignancies for ≤3 years before trial accrual, with the exception of currently treated basal cell or squamous cell carcinoma of the skin, or in situ carcinoma of the cervix or breast. Patients were required to comply with the lenalidomide risk management plan for pregnancy prevention.[2]

Principal exclusion criteria included: use of an experimental drug or experimental medical device within 4 weeks of planned treatment initiation; pregnancy or lactation in female patients; a history of central nervous system involvement with lymphoma; a history of clinically relevant liver or renal insufficiency, or of significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances; a history of other concurrent severe and/or uncontrolled medical condition(s) that could cause unacceptable safety risks or compromise compliance with the protocol (for example, uncontrolled diabetes mellitus or active or uncontrolled infections, such as human immunodeficiency virus, hepatitis B virus, or hepatitis C virus); and previous treatment with bendamustine and/or lenalidomide.

Statistical methods

All authors had access to the primary clinical trial data. Data analyses were carried out by JC. Hypotheses were based on activity data obtained with bendamustine in combination with rituximab, plus lenalidomide monotherapy, in patients with mantle cell lymphoma (MCL).[3–8] It was hypothesized that adding lenalidomide to bendamustine plus rituximab may increase the complete response (CR) rate by 20% (from 40% to 60%), with a significance level alpha of 0.05, and 80% power. The required sample size for this single-stage design was 42 patients. If ≥23 patients (55%) achieved a CR at the end of the consolidation phase, the primary end point of the trial would have been reached. It was expected that around 75–80% of patients (*n* = 32–34) would achieve a CR or partial response. The expected 2-year progression-free survival (PFS) in these patients without maintenance therapy was around 25%. Assuming that 30 patients entered the maintenance phase, and that rituximab, lenalidomide, and bendamustine (R2B) produced an absolute increase in PFS at 2 years of at least 20% (increase from 25% to 45%), the statistical power of the trial would be 88% with a one-sided alpha error of 0.05, accrual of 18 months, and follow-up of 36 months.

Patients who received at least one dose of trial medication were evaluated for efficacy and safety. Patients who achieved an overall response and received lenalidomide maintenance treatment were assessed for all efficacy and long-term side-effect end points. Baseline characteristics, efficacy end points, and safety end points were presented for all patients. Discrete variables were summarized by frequencies and percentages. Continuous variables were summarized using standard measures of central tendency and dispersion (mean and standard deviation, or median and interquartile range). Time-to-event variables (PFS and overall survival) were analyzed using Kaplan–Meier methodology.

Efficacy and safety assessments

Treatment response was assessed by: physical examination; CT and positron emission tomography (PET)-CT scan; bone marrow (BM) evaluation (histology, flow cytometry, immunohistochemistry, and molecular biology); blood cell counts; and gut endoscopy (in selected patients). Response and progression were defined according to Cheson criteria,[9] using the same imaging methods (CT or PET-CT scans) that had been employed for baseline tumor measurements. Response was assessed after cycles 2 and 4 of the induction phase, after cycle 2 of the consolidation phase, and every 3 months from the beginning of maintenance treatment until the end of month 24. During the follow-up phase response assessment was evaluated by CT scan on month 30, 36 and 42.

Baseline BM and PB samples were screened for a molecular marker and, if the results were negative, an additional screening was performed on the diagnostic lymph node specimen, if available. MRD was then assessed in both BM and PB samples (only in patients with an available marker) at the end of the induction phase (month 4), at the end of the consolidation phase (month 6), and subsequently at months 12, 18, and 24 from the beginning of therapy.

The safety population included all patients who received at least one dose of trial medication and at least one follow-up assessment. Safety was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Second primary malignancies (hematologic or non-hematologic) occurring at any time up to the end of the follow-up period were monitored as events of interest, and reported as serious AEs.

Prevention of infections

- *Antiviral prophylaxis* with acyclovir 800 mg at day or valaciclovir 500 mg at day throughout the study period;
- *Anti bacterial prophylaxis* with levoxacine or ciprofloxacine will be administrated in case of neutropenia <1.0 x 10^9/l;

- *Cotrimoxazole BACTRIM F* 1 tablet x 2/daily for two consecutive days/week or Pentamidine aerosol every 15 days in patients with Bactrim allergy or in patients with G6PD deficiency throughout the study period;
- *Immunoglobulin* in case of IgG level < 0.3-0.5 gr/dl and frequent infectious events;

DOSE MODIFICATION OF STUDY TREATMENTS ACCORDING TO THE STUDY PROTOCOL

INDUCTION PHASE

Lenalidomide dose modification according to hematological and extrahematological toxicity is allowed. Those patients for whom Lenalidomide dose reduction is not sufficient and require also a reduction in the dose of Bendamustine, they will interrupt treatment, they will be considered failure and they will be treated according to the single centre policy.

The new cycle of treatment may begin on the scheduled day 1 if:

• The ANC is $\geq 1.5 \times 10^9$/L;

• The platelet count is $\geq 75 \times 10^9$/L;

• Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ grade 1 severity;

• Any other R2-B related AE not requiring discontinuation has resolved to ≤ grade 2 severity.

If these conditions are not met on day 1 of a new cycle, the patient will be evaluated at least once every seven days and a new cycle of R2B will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the FIL Medical Monitor must be notified.

If Lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. No dose (re-)escalation is permitted at any time.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 50 mL/min] will receive a lower dose of Lenalidomide of 5 mg p.o. on day 1 to 14 of a 28 days course.

Lenalidomide dose modification

Extra-haematological toxicity

All patients who experience ≥ grade 3 extra-haematological toxicity suspend treatment until resolution to ≤ grade 2 toxicity. Incremental (5 mg) dose reduction is allowed for ≥ grade 3 extra-haematological toxicity. Patients who can not tolerate the dose of 5 mg daily will prosecute the induction phase only with Rituximab and Bendamustine.

Haematological toxicity.

Neutropenia. All patients who experience either: a) sustained (≥ 7 days) grade 3 neutropenia; b) grade 3 neutropenia with fever (temperature ≥ 38.5°C); grade 4 neutropenia, suspend treatment. Treatment will be resumed at the same dosage (with G-CSF support, if needed) when neutropenia < grade 2 and infection resolved. For recurrent grade 4 neutropenia, dose will be reduced by 5 mg in subsequent cycles. Patients who can not tolerate the dose of 5 mg daily will prosecute the induction phase only with Rituximab and Bendamustine.

Thrombocytopenia. All patients who experience ≥ grade 3 suspend treatment. Treatment will be resumed if thrombocytopenia resolve to < grade 2 and dose will be reduced by 5 mg in subsequent cycles. The minimum dose permitted is 5 mg daily. Patients who can not tolerate the dose of 5 mg daily will prosecute the induction phase only with Rituximab and Bendamustine.

Table 1. Lenalidomide dose modification

NCI CTCAE Toxicity Grade	ACTION REQUIRED
Sustained (≥ 7 days) grade 3 neutropenia or ≥ grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or grade 4 neutropenia	• Hold (interrupt dose). • Follow CBC at least every seven days. • If neutropenia has resolved to < grade 2 restart at next lower dose level. • Use of growth factors (G-CSF) is permitted at the discretion of the investigator
Thrombocytopenia ≥ grade 3 (platelet count < 50 x 10^9/L)	• Hold (interrupt dose). • Follow CBC weekly every seven days. • If thrombocytopenia resolves to ≥ 75 x 10^9/L restart at

	next lower dose level.
Venous thrombosis/embolism ≥ grade 3	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
ALT > 3 but ≤ 5 x ULN and total bilirubin of ≥1.5 x ULN or ALT > 5 x ULN, and/or total bilirubin ≥ 1.5 x ULN	• Hold (interrupt) and weekly testing performed until the ALT and the total bilirubin returns to baseline • No change in dose is recommended if recovery from the event occurs within ≤ 14 days period. • If recovery is prolonged, >14 days, decrease by one dose level and weekly testing of liver functions during that cycle should occur. Notify medical monitor if the values do not return to baseline within 28 days
Peripheral Neuropathy= grade 3	• Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ Grade 1).
Peripheral Neuropathy= grade 4	• Discontinue study drug and discontinue patient from study.
Other ≥ grade 3 lenalidomide-related adverse events	• Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ grade 2)

Table 2: Dose modification steps for patients who need Lenalidomide dose modifications during the induction phase

Planned dose	**Modified dose**
10 mg daily on Days 1-14, every 28 days	5 mg daily on Days 1-14, every 28 days
5 mg daily on Days 1-14, every 28 days	No treatment with Lenalidomide

Bendamustine dose modification

Bendamustine dose reduction is not allowed. In case of persistent toxicity after having fulfilled Lenalidomide dose reduction, patients will interrupt treatment, they will be considered failure and they will be treated according to the single centre policy.

Rituximab dose modification

Rituximab dose reduction is not planned.

CONSOLIDATION PHASE

The new cycle of treatment may begin on the scheduled day 1 if:

• The ANC is ≥ 1.5 x 10^9/L;

• The platelet count is ≥ 75 x 10^9/L;

• Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ grade 1 severity;

• Any other R2 related AE not requiring discontinuation has resolved to ≤ grade 2 severity.

If these conditions are not met on day 1 of a new cycle, the patient will be evaluated at least once every seven days and a new cycle of R2 will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the FIL Medical Monitor must be notified.

If Lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. No dose (re-)escalation is permitted at any time.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower dose of Lenalidomide of 10 mg p.o. on day 1 to 21 of a 28 days course

Lenalidomide dose modification

Extra-haematological toxicity.

All patients who experience ≥ grade 3 extra-haematological toxicity suspend treatment until resolution to ≤ grade 2 toxicity. Incremental (5 mg) dose reduction is allowed for ≥ grade 3 extra-haematological toxicity. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

Haematological toxicity.

Neutropenia. All patients who experience either: a) sustained (≥ 7 days) grade 3 neutropenia; b) grade 3 neutropenia with fever (temperature ≥ 38.5°C); grade 4 neutropenia, suspend treatment. Treatment will be resumed at the same dosage (with G-CSF support, if needed) when neutropenia < grade 2 and infection resolved. For recurrent grade 4 neutropenia, dose will be reduced by 5 mg in subsequent cycles. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

Thrombocytopenia. All patients who experience ≥ grade 3 suspend treatment. Treatment will be resumed if thrombocytopenia resolve to < grade 2 and dose will be reduced by 5 mg in subsequent cycles. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

Table 3: Dose modification steps for patients who need Lenalidomide dose modifications during the consolidation phase

Planned dose	**Modified dose**
15 mg daily on Days 1-21, every 28 days	10 mg daily on Days 1-21, every 28 days
10 mg daily on Days 1-21, every 28 days	5 mg daily on Days 1-21, every 28 days
5 mg daily on Days 1-21, every 28 days	No treatment with Lenalidomide

Rituximab dose modification

Rituximab dose reduction is not planned.

MAINTENANCE PHASE

The new cycle of treatment may begin on the scheduled day 1 if:

• The ANC is ≥ 1.5 x 10^9/L;

• The platelet count is ≥ 75 x 10^9/L;

• Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ grade 1 severity;

• Any other R2 related AE not requiring discontinuation has resolved to ≤ grade 2 severity.

If these conditions are not met on day 1 of a new cycle, the patient will be evaluated at least once every seven days and a new cycle of R2 will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the FIL Medical Monitor must be notified.

If Lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level

will be initiated on day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. No dose (re-)escalation is permitted at any time.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower dose of Lenalidomide of 10 mg p.o. on day 1 to 21 of a 28 days course

Lenalidomide dose modification

Extra-haematological toxicity.

All patients who experience ≥ grade 3 extra-haematological toxicity suspend treatment until resolution to ≤ grade 2 toxicity. Incremental (5 mg) dose reduction is allowed for ≥ grade 3 extra-haematological toxicity. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

***Haematological toxicity*.**

Neutropenia. All patients who experience either: a) sustained (≥ 7 days) grade 3 neutropenia; b) grade 3 neutropenia with fever (temperature ≥ 38.5°C); grade 4 neutropenia, suspend treatment. Treatment will be resumed at the same dosage (with G-CSF support, if needed) when neutropenia < grade 2 and infection resolved. For recurrent grade 4 neutropenia, dose will be reduced by 5 mg in subsequent cycles. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

Thrombocytopenia. All patients who experience ≥ grade 3 suspend treatment. Treatment will be resumed if thrombocytopenia resolve to < grade 2 and dose will be reduced by 5 mg in subsequent cycles. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment.

Supplementary Table 1. Previous history of treatment and response

	No.	% of total population (N = 42)
Previous first-line chemotherapy treatment		
R-CHOP (like) + R-VNCOP	27	64
R-CVP	2	5
R-ARA-C based therapy	11	26
R-FC	2	5
Frontline ASCT	10	24
Response to first-line therapy		
CR	30	71
PR	8	19
SD	2	5
PD	2	5
Duration of response to first-line therapy		
Primary refractory	4	10
<12 months	11	26
>12 to <24 months	12	29
>24 months	14	33
Unknown	1	2
Duration of response, months		
Median	19	
Range	2-85	

ASCT, autologous stem cell transplant; CR, complete response; PD, progressive disease; PR, partial response; R-ARA-C, rituximab with cytarabine; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab with cyclophosphamide, vincristine and prednisone; R-FC, rituximab with fludarabine and cyclophosphamide; R-VNCOP, rituximab with etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, and bleomycin; SD, stable disease.

Supplementary Table 2. Grade 3/4 adverse events by treatment phase

	Induction + consolidation (n = 42)				Maintenance (n = 28)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Neutropenia	13	31	17	40	10	36	10	36
Thrombocytopenia	5	12	1	2	2	7	0	0
Febrile neutropenia	4	10	0	0	1	4	1	4
Anemia	2	5	0	0	1	4	0	0
Nephrotoxicity	2	5	0	0	0	0	0	0
Infections	1	2	0	0	2	7	0	0
Pulmonary toxicity	1	2	2	5	0	0	0	0
Cardiotoxicity	1	2	0	0	0	0	0	0
Urticaria	1	2	0	0	0	0	0	0
Syncope	1	2	0	0	0	0	0	0
Liver toxicity*	1	2	0	0	0	0	0	0
Ipomagnesemia	1	2	0	0	0	0	0	0
Tumor lysis syndrome	0	0	1	2	0	0	0	0
GI toxicity	0	0	0	0	1	4	0	0
Neurotoxicity	0	0	1	2	1	4	0	0
Edema	0	0	0	0	1	4	0	0
Fatigue	0	0	0	0	1	4	0	0

GI, gastrointestinal.
*Increased gamma-glutamyltransferase level

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