RELEVANCE: A phase 3 randomised study comparing efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy in first-line patients with follicular lymphomat

M. André

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1. Objectives of the trial

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG criteria.

The secondary objectives of the study are:

1. To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy.
2. Time to Treatment Failure (TTF), Event Free Survival (EFS), Time to Next Anti-Lymphoma Treatment (TTNLT), Time to Next Chemotherapy Treatment (TTNCT), Overall Survival (OS) and ORR rate at 120 weeks by IWG 1999 criteria.
3. Health related quality of life as measured by the EORTC QLQ- C30.
4. To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.

2. Research plan and methods

2.1 Major inclusion criteria

- Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators.
- Have no prior systemic treatment for lymphoma.
- Must be in need of treatment as evidenced by at least one of the following criteria:
  1. Bulky disease defined as: 1) a nodal or extra nodal (except spleen) mass >7cm in its greater diameter or, 2) involvement of at least three nodal or extra nodal sites (each with a diameter greater than >3 cm).
  2. Presence of B symptoms.
  3. Symptomatic splenomegaly.
  4. Compression syndrome (ureteral, orbital, gastrointestinal).
  5. Any one of the following cytopenias due to lymphoma: 1) hemoglobin <10g/dL (6.25 mmol/L) 2) platelets <100 x 109/L, or 3) absolute neutrophil count (ANC) <1.5 x 109/L.

Author: M. André, MD, Department of Hematology, CHU UCL Mont Godinne Dinant, Yvoir, Belgium.

Please send all correspondence to: M. André, MD, CHU UCL Mont Godinne Dinant, Department of Hematology, Avenue G. Thérasse 1, 5530 Yvoir, Belgium, tel: +32 81 423864, email: marc.andre@uclouvain.be.

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6. Pleural or peritoneal serous effusion or (irrespective of cell content).

Bi-dimensionally measurable disease with at least one mass lesion >2 cm that was not previously irradiated.

7. Stage II, III or IV disease.
8. Adequate hematological function (unless abnormalities are related to lymphoma infiltration of the bone marrow) within 28 days prior to signing informed consent.

2.2 Major exclusion criteria

- Clinical evidence of transformed lymphoma by investigator assessment.
- Grade 3b follicular lymphoma.
- Patients taking corticosteroids during the last four weeks, unless administered at a dose equivalent to <10 mg/day prednisone (over these four weeks).
- Major surgery (excluding lymph node biopsy) within 28 days prior to signing informed consent.
- Seropositive for or active viral infection with hepatitis B or C virus and HIV.

2.3 Study population and Belgian specific contribution

Total number of patients in the study is 1,000. According to our previous experience with the PRIMA trial in Belgium on the same patients population, approximately 100 patients should be recruited in Belgium.

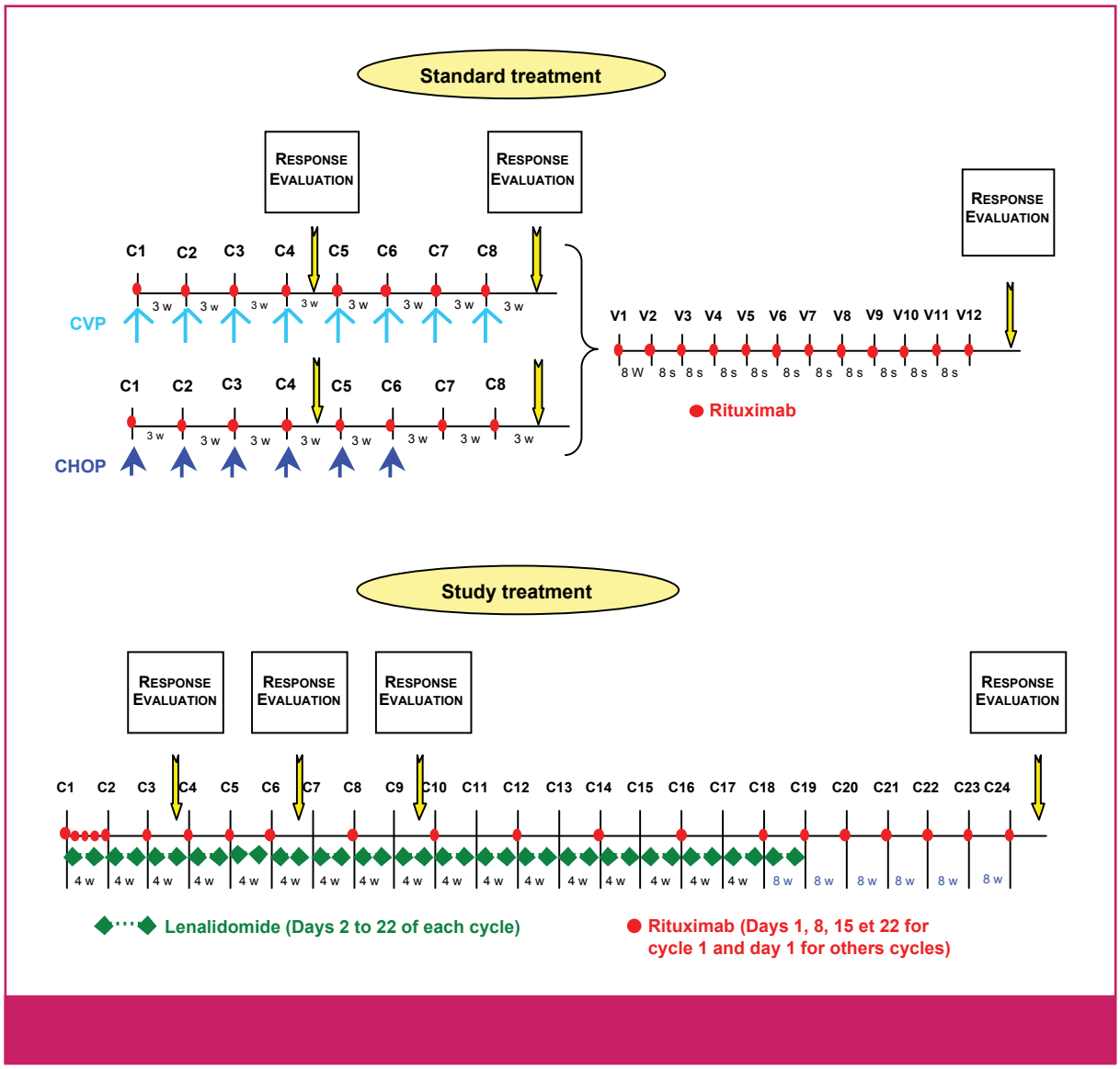

Figure 1. Legend: Scheme of the Relevance trial.
(w: weeks, c: cycle, v: visit, CHOP: cyclophosphamide, Adriamycin, vincristine, prednisone, CVP: cyclophosphalmide, vincristine, prednisone)

3. List of the Belgian centres

Centre	Last name	First name
CHU UCL Mont-Godinne Dinant	ANDRE	Marc
Institut Jules Bordet	BRON	Dominique
Heilig Hart Ziekenhuis	DEMUYNCK	Hilde
Centre Hospitalier Jolimont - Lobbes	STRAETMANS	Nicole
Clinique Saint Joseph	BOULET	Dominique
CHU Ambroise Paré	ROBIN	Valérie
RHMS	DEWEWEIRE	Anne
Hôpital Sainte Elisabeth	MATHIEUX	Valérie
CHU De Liège	BONNET	Christophe
Clinique Saint Joseph Liège	LONGREE	Luc
AZ VUB	TRULLEMANS	Fabienne
Clinique Saint-Pierre	CONNEROTTE	Thierry
UZ Gent	OFFNER	Fritz
Cliniques Sud Luxembourg	PIERRE	Pascal
Grand Hôpital de Charleroi	PRANGER	Delphine
UCL, Saint Luc	VAN DEN NESTE	Eric
AZ Groeninge	VAN EYGEN	Koenraad
A. Z. Sint-Jan	VAN HOOF	Achiel
CHR Peltzer La Tourelle	VANSTRAELEN	Gaëtan
CHWAPI, Tournai	KARGAR-SAMANI	Khalil
CHU Sart Tilman	BONNET	Christophe
ZNA Stuivenberg	ZACHEE	Pierre
CHR Citadelle	JACQUY	Caroline
Hôpital Erasme	MAEREVOET	Marie

4. Feasibility

The duration of the entire study will be approximately twelve to thirteen years. Patients receive two-four weeks of screening, approximately two and a half years of treatment and up to ten years of follow-up. The expected accrual duration is 40 months.

This trial, if positive, would change the standard of care for first-line treatment of patients with follicular lymphoma. A therapy with Rituximab and lenalidomide could be a major improvement in the quality of life for patients suffering from follicular lymphoma.