Extended Dosing of Lenalidomide and Intensified Rituximab in Untreated Indolent Lymphoma, Results of a Phase II Study.

Nathan Fowler, Chan Yoon Cheah, Sattva Neelapu, Loretta Nastoupil, Francesco Turturro, Fredrick Hagemeister, Larry W. Kwak, Jorge Romaguera, Michelle Fanale, Luis Fayad, Linda Claret, Lei Feng, Eric Davis, and Felipe Samaniego

Department of Lymphoma/Myeloma, UT MD Anderson Cancer Center, 1515 Holcombe Blvd Houston TX 77030 USA

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Introduction

- Lenalidomide is active in relapsed NHL, and rituximab (R) is effective alone and in combination with chemotherapy.
- Phase II studies have shown significant activity of the combination of lenalidomide and R (R2) in untreated indolent NHL but the optimal schedule and length of dosing is yet to be determined. (Fowler et al., 2014, Kimby et al., 2014, Martin et al., 2014)
- The aim of this study was to evaluate the efficacy and safety of extended dosing of lenalidomide with early rituximab intensification in untreated low grade lymphoma.

Methods

- We included pts with measurable (>1.5 cm) untreated SLL and FL
- Dosing schema is displayed in **Figure 1**
- Patients with SLL started at 10mg of lenalidomide, with monthly dose escalation.
- Prophylactic growth factors were not used.
- Response was assessed every 3 cycles using 1999 International Working Group Response Criteria (Cheson et al., 1999)

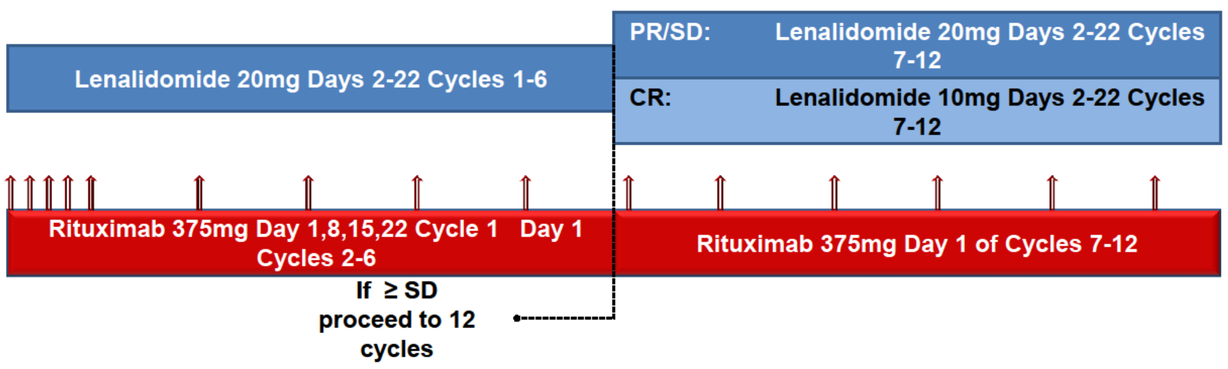

Figure 1. Treatment schema for extended dosing with lenalidomide and rituximab.

Results

- 45 patients were enrolled, with 44 evaluable for response
- The median follow-up is 37 (range 1 - 41) months
- Baseline characteristics are displayed in **Table 1.**
- Response rates were better amongst patients with FL and deepened over time (**Figure 2A,B**)

	FL	SLL
number of patients	30	15
median age (range), years	57 (28 - 80)	59 (44- 76)
female (%)	17 (57%)	5 (33%)
stage 3 **stage 4**	12 (40%) 18 (60%)	0 (0%) 15 (100%)
B symptoms	4 (13%)	3 (20%)
hemoglobin <120g/L	1 (3%)	3 (20%)
elevated serum LDH	1 (3%)	1 (7%)
FLIPI low **FLIPI intermediate** **FLIPI high**	5 (17%) 19 (63%) 6 (20%)	-
GELF high tumor burden	26 (87%)	-

Table 1. Baseline characteristics of patients

histology	CR/CRu	PR	SD	PD	3y PFS (95%CI)
FL	29 (97%)	1 (3%)	0 (0%)	0 (0%)	97% (78-100%)
SLL*	5 (35%)	6 (43%)	2 (14%)	0 (0%)	48% (17–74%)

Table 2. Best response and PFS by histology. All patients alive at date of last follow-up.
*one pt with SLL was not evaluable for response

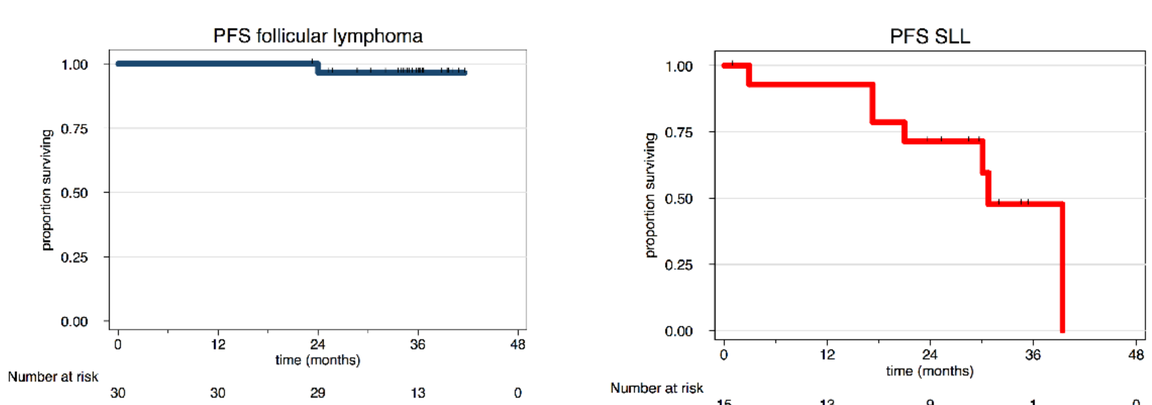

Figure 2. Progression free survival by histology

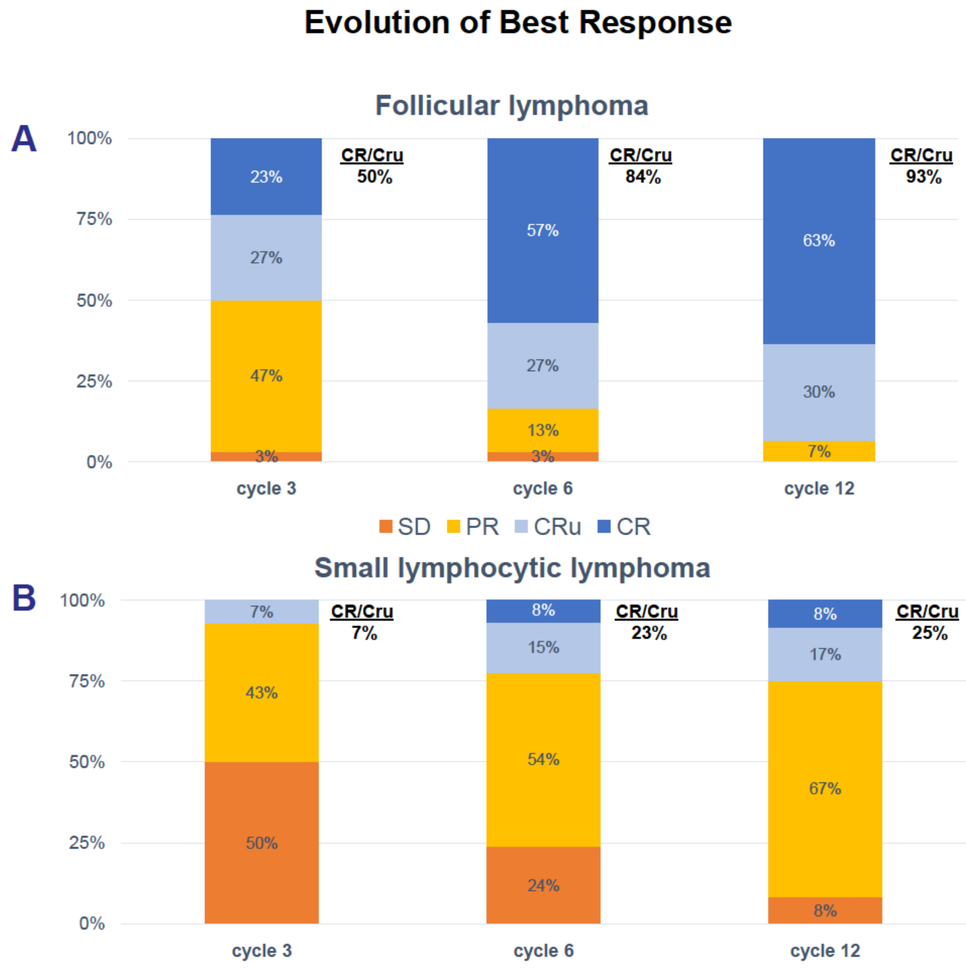

Figure 3. Response rates amongst patients with Follicular lymphoma (**A**) and small lymphocytic lymphoma (**B**) after 3, 6 and 12 cycles of therapy

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hematologic					
Anemia	11 (24%)	3 (7%)	0 (0%)	0 (0%)	**14 (31%)**
Neutropenia	6 (13%)	3 (7%)	6 (13%)	24 (53%)	**41 (91%)**
Thrombocytopenia	18 (40%)	3 (7%)	2 (4%)	0 (0%)	**23 (51%)**
Non-Hematologic					
Constipation	18 (40%)	9 (20%)	0 (0%)	0 (0%)	**27(60%)**
Cough/Dyspnea	19 (42%)	8 (18%)	1 (2%)	0 (0%)	**28 (62%)**
Dermatology/Skin	3 (7%)	1 (2%)	2 (4%)	0 (0%)	**6 (13%)**
Diarrhea	20 (44%)	14 (31%)	3 (7%)	0 (0%)	**37 (82%)**
Dizziness	13 (29%)	3 (7%)	2 (4%)	0 (0%)	**18 (40%)**
Edema	16 (36%)	4 (9%)	1 (2%)	0 (0%)	**21 (47%)**
Eye Irritation	23 (51%)	9 (20%)	0 (0%)	0 (0%)	**32 (71%)**
Fatigue	11 (24%)	24 (53%)	6 (13%)	0 (0%)	**41 (91%)**
Fever	7 (16%)	1 (2%)	1 (2%)	0 (0%)	**10 (22%)**
Memory Impairment	11 (24%)	7 (16%)	0 (0%)	0 (0%)	**18 (40%)**
Mucositis	18 (40%)	3 (7%)	0 (0%)	0 (0%)	**21 (47%)**
Musculoskeletal	7 (16%)	5 (11%)	1 (2%)	0 (0%)	**13 (29%)**
Nausea/Vomiting	12 (27%)	12 (27%)	1 (2%)	0 (0%)	**25 (56%)**
Neurology	21 (47%)	5 (11%)	0 (0%)	0 (0%)	**26 (58%)**
Pain/Myalgia	17 (38%)	16 (36%)	3 (7%)	0 (0%)	**37 (82%)**
Rash	12 (27%)	5 (11%)	6 (13%)	0 (0%)	**23 (51%)**
Upper Respiratory Infection	0 (0%)	12 (27%)	1 (2%)	0 (0%)	**13 (29%)**

Table 2. Toxicities, worst grade per patient.

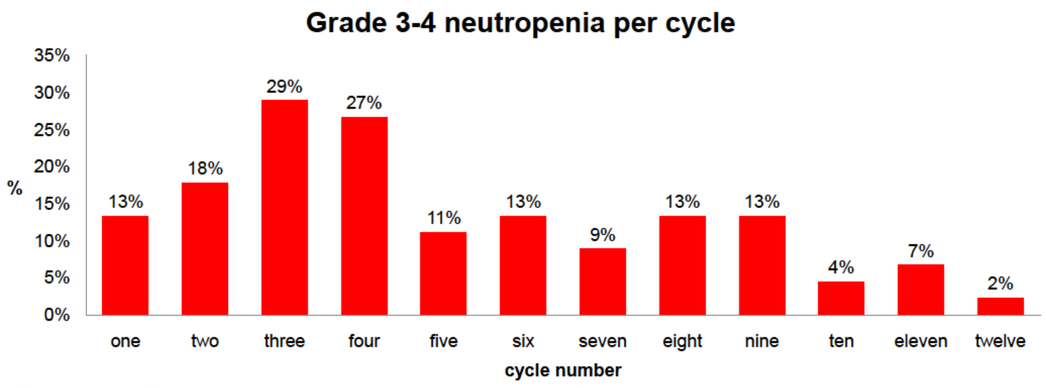

Figure 4. Percentage of patients with grade 3-4 neutropenia, per treatment cycle

Conclusion

- Extended dosing of R2 with rituximab intensification results in prolonged disease control in indolent NHL.
- This approach is also associated with increased but manageable hematologic toxicity.
- Ongoing phase III studies based upon this schedule are underway in untreated follicular lymphoma.

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Indolent lymphoma

Nathan Fowler

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