INTERVIEW

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Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2, 5

DR LOVE: Would you review your Phase III trial in indolent lymphoma evaluating bendamustine/rituximab (BR) versus R-CHOP?

PROF RUMMEL: The Study group indolent Lymphomas (StiL) designed a pivotal Phase III trial comparing BR to R-CHOP. Compared to R-CHOP, BR demonstrated much lower toxicity and better efficacy (Rummel 2009; [1.1]).

1.1

Efficacy and Safety of BR versus R-CHOP as Initial Therapy for FL, Indolent Lymphomas and MCL

	BR (n = 260)	R-CHOP (n = 253)	*p*-value
Overall response	92.7%	91.3%	—
Complete response	39.6%	30.0%	0.0262
Progression-free survival	54.9 months	34.8 months	0.00012
Grade III/IV neutropenia (% of cycles)	10.7%	46.5%	<0.0001
Infectious complications	36.9%	50.2%	0.0025
Peripheral neuropathy	6.9%	28.8%	<0.0001
Stomatitis	6.2%	18.6%	<0.0001
Allergic reaction (skin)	15.4%	5.9%	0.0003

Rummel MJ et al. Presentation. *Proc ASH* 2009;**Abstract 405**.

Tracks 3, 6, 12

DR LOVE: What about BR in elderly patients?

PROF RUMMEL: A Phase II study of BR for an elderly patient population (over age 75) (Rummel 2008; [1.2]) demonstrated good efficacy and acceptable toxicity. For patients with renal insufficiency, bendamustine is one of the best recommendations.

DR LOVE: Would you discuss the additional data you presented from the BR/R-CHOP study at the ASCO/ASH Joint Session?

PROF RUMMEL: A separate efficacy analysis for each of the subpopulations with FL, marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM) and MCL was presented. Among patients in each of the FL (Rummel 2010; [1.3]), WM and MCL subpopulations, progression-free survival is significantly improved with BR.

DR LOVE: Does BR have an impact on stem cell collection?

PROF RUMMEL: The ability to mobilize stem cells in patients receiving this regimen has been examined (Burchardt 2009), and we have evidence that it is indeed possible to mobilize stem cells after a patient has received BR.

1.2

Phase II Study of BR for Elderly Patients (Over Age 75) with Indolent Lymphomas or Mantle-Cell Lymphoma (n = 26)

Median age	Overall response	Complete response
79 years	88%	35%

Rummel MJ et al. *Proc ASCO* 2008;**Abstract 8572**.

1.3

Efficacy of BR versus R-CHOP in the FL Subpopulation (n = 279)

	BR	R-CHOP	Hazard ratio	*p*-value
Progression-free survival (months)	Not reached	46.7	0.63	0.0281

Rummel MJ et al. Presentation. *Proc ASH* 2009;**Abstract 405**.

Track 9

DR LOVE: Could you discuss the research your group is doing on bortezomib in indolent lymphomas?

PROF RUMMEL: A Phase II trial with single-agent bortezomib demonstrated that bortezomib has modest activity as a single agent and has the potential to be combined with other agents for low-grade lymphomas (Di Bella 2010; [1.4]).

A Phase II study with a combination of bortezomib, bendamustine and rituximab (VBR) has been presented (Fowler 2009; [1.5]) and has shown that the combination is feasible with promising results.

In view of this, StiL is planning to initiate a large, randomized Phase III study comparing BR to VBR in relapsed FL, MZL and WM. This study will evaluate the benefit of bortezomib added to BR. A similar Phase III Austrian study is being conducted in MCL.

1.4

Efficacy of Single-Agent Bortezomib in a Phase II Study in Relapsed or Refractory Indolent Lymphomas*

Overall response	Stable disease	Median time to response	Median duration of response	Median survival	Median progression-free survival
13.3%	64.2%	2.2 months	7.9 months	27.7 months	5.1 months

* n = 53 of 59 evaluable patients who completed more than two cycles

Di Bella N et al. *Blood* 2010;115(3):475–80.

1.5

Phase II VERTICAL Study: Efficacy and Safety of Bortezomib/Bendamustine/Rituximab in Relapsed or Refractory Follicular Lymphoma*

Overall response	Complete response	Partial response	≥Grade III peripheral neuropathy
86%	53%	34%	10%

* n = 59 of 63 patients with at least one postbaseline response assessment

Fowler N et al. *Proc ASH* 2009;**Abstract 933**.

Track 14

DR LOVE: What are your thoughts on rituximab maintenance in FL?

PROF RUMMEL: The Phase III PRIMA study evaluating maintenance rituximab after initial rituximab/chemotherapy induction in FL has now been presented (Salles 2010; [1.6]). More than 1,000 patients were randomly assigned to maintenance therapy with rituximab — one dose every two months for two years — or observation.

The magnitude of difference in progression-free survival was clinically relevant and much higher than I had anticipated, primarily because a good progression-free survival is achieved with rituximab/chemotherapy induction alone.

Slightly more side effects occurred with rituximab maintenance than on the observation arm (Salles 2010; [1.7]). The infection rate is slightly higher and a few more cytopenias occur. However, the progression-free survival clearly favors the rituximab maintenance arm, and the higher incidence of cytopenias and infections did not affect the progression-free survival benefit.

1.6

Phase III PRIMA Study: Efficacy Results with Rituximab Maintenance in Previously Untreated FL

	Observation (n = 513)	Rituximab maintenance (n = 505)	Hazard ratio	*p*-value
Two-year PFS	66%	82%	0.50	<0.0001

PFS = progression-free survival

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

1.7

Phase III PRIMA Study: Safety Events

	Observation (n = 508)	Rituximab maintenance (n = 501)
Grade III/IV infections	<1%	4%
Grade ≥II infections	22%	37%
Grade III/IV neutropenia	<1%	4%

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

Track 13

DR LOVE: What about duration of rituximab maintenance and maintenance after initial induction with BR?

PROF RUMMEL: We are addressing these questions in a StiL-sponsored study in Germany. Patients initially receive BR as up-front therapy and are then randomly assigned to either two or four years of rituximab maintenance (1.8). ■

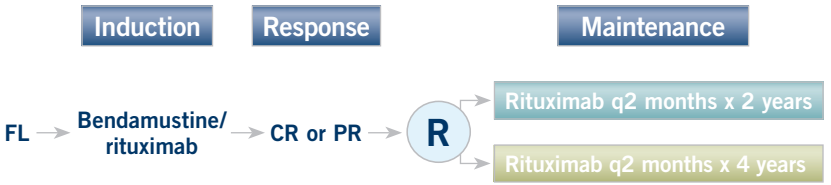
1.8

StiL MAINTAIN Phase III Study: Significance of Duration of Maintenance Therapy with Rituximab in Non-Hodgkin's Lymphoma

Protocol ID: StiL NHL 7-2008 **Target Accrual:** 874

Eligibility

- FL, immunocytoma, CLL without leukemic hemogram, marginal zone lymphoma or MCL
- No prior systemic therapy



FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; MCL = mantle-cell lymphoma; CR = complete response; PR = partial response

www.clinicaltrials.gov. Accessed September 10, 2010.

SELECT PUBLICATIONS

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

Di Bella N et al. **Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma.** *Blood* 2010;115(3):475-80.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL study.** *Proc ASH* 2009;**Abstract 933**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL.** Presentation. ASCO/ASH Joint Session 2010. No abstract available

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Rummel MJ et al. **Efficacy and safety of bendamustine and rituximab in the treatment of indolent and mantle cell lymphomas in older patients.** *Proc ASCO* 2008;**Abstract 8572**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.