INTERVIEW

Nathan H Fowler, MD

Dr Fowler is Co-Director of Clinical and Translational Research in the Department of Lymphoma/Myeloma at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-14

Track 1 Mechanism of action of lenalidomide and synergy with rituximab in lymphoma

Track 2 Mechanism of action of the type II anti-CD20 monoclonal antibody obinutuzumab

Track 3 Development of the R^2 regimen of lenalidomide/rituximab in indolent lymphoma or MCL

Track 4 RELEVANCE: A Phase III trial of R^2 versus rituximab-based chemotherapy → rituximab maintenance for previously untreated FL

Track 5 Results from the StiL NHL 1-2003 and BRIGHT studies of BR in previously untreated indolent or mantle-cell lymphomas

Track 6 Activity of R^2 in indolent lymphomas and CLL

Track 7 Clinical experience with lenalidomide for B-cell lymphomas

Track 8 Activity of the BTK inhibitor ibrutinib and the PI3K delta inhibitor idelalisib in B-cell NHL

Track 9 Rasburicase for tumor lysis syndrome and tumor flare in aggressive lymphomas and CLL

Track 10 **Case discussion:** A 52-year-old patient with composite FL (80% Grade I/II, 20% Grade IIIb) achieves a complete remission with R-CHOP

Track 11 **Case discussion:** An 81-year-old patient with asymptomatic Grade I/II FL initially undergoes observation

Track 12 **Case discussion:** A 62-year-old patient who received BR 5 years ago for Stage III FL presents with recurrent disease in the neck and groin

Track 13 Criteria for assessing risk in patients with MCL

Track 14 Use of endoscopy to assess response in the colon in patients with MCL

Select Excerpts from the Interview

Tracks 3-4

DR LOVE: Would you discuss the background for the study of the lenalidomide/rituximab (R^2) regimen for indolent lymphomas?

DR FOWLER: Initially we launched a pilot study of the R^2 regimen based on results from studies in mantle-cell lymphoma (MCL) cell lines and mouse models showing that it produced better results than either agent alone. This pilot study was for 30 patients with treatment-naïve indolent lymphomas.

Early on we observed a strong signal in FL. In fact, when we first presented the data about 3 years ago, the complete response rate for FL was 100%. So the study was expanded to enroll about 110 patients, especially those with FL (Fowler 2012; [5.1]), and in this population the complete response rate for patients with FL was 87%.

5.1

Efficacy and Safety Results of the Phase II Trial of Lenalidomide and Rituximab for Patients with Untreated Indolent Lymphomas

Efficacy	FL (n = 46)	SLL (n = 30)	MZL (n = 27)	All patients (n = 103)
Overall response rate	98%	80%	89%	90%
CR/CRu	87%	27%	67%	64%
PR	11%	53%	22%	26%
Stable disease	2%	13%	11%	8%
Progressive disease	0%	7%	0%	2%
Two-year PFS*	89%	NR	NR	83%
Safety	**All patients**			
Neutropenia	40%			
Thrombocytopenia	6%			

FL = follicular lymphoma; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; CR = complete response; CRu = unconfirmed CR; PR = partial response; PFS = progression-free survival; NR = not reported

* Median follow-up of 22 months

Fowler N et al. *Proc ASH* 2012;**Abstract 901**.

That was the basis for the ongoing Phase III RELEVANCE trial for patients with previously untreated FL (NCT01650701). Patients are randomly assigned to receive R[2] or rituximab/chemotherapy, including R-CHOP, R-CVP or rituximab/bendamustine (BR), followed by rituximab maintenance therapy. We hope that biologic treatment with an immune-modulated antibody will produce better results than any of the 3 common choices of standard chemotherapy.

Track 5

DR LOVE: In general practice, what is the most commonly used first-line rituximab-based chemotherapy regimen outside of a trial setting?

DR FOWLER: The results of the randomized STiL trial for patients with newly diagnosed low-grade NHL or MCL demonstrated a dramatically longer progression-free survival and less myelosuppression with BR than with R-CHOP (Rummel 2013; [5.2]). We've seen a rapid paradigm shift in the way newly diagnosed FL is treated. Based on my experience with patients referred from community oncologists and in the practices of my colleagues, I believe BR has replaced R-CHOP as the new standard for indolent disease.

It is important to clarify whether the disease has undergone transformation or if it has any Grade III components, in which case I treat with R-CHOP. I believe that for higher-grade lymphomas BR is equivalent to R-CHOP, although we don't have enough data to support this.

DR LOVE: What is your view on the preliminary results of the BRIGHT trial of BR presented at ASH 2012 (Flinn 2012; [5.2])?

DR FOWLER: We don't have the progression-free survival data from the BRIGHT study yet. From the preliminary results, BR appears to be similar in efficacy to

5.2

Phase III Study Results with Bendamustine/Rituximab (BR) versus Standard First-Line Chemotherapy for Indolent and Mantle-Cell Lymphomas

	BRIGHT[1]		StiL NHL 1-2003[2]	
Efficacy	**BR** (n = 213)	**R-CHOP/R-CVP** (n = 206)	**BR** (n = 261)	**R-CHOP** (n = 253)
Overall response rate	94%	84%	93%	91%
Complete response rate (all)	31%	25%	40%	30%
	HR, 1.26; $p = 0.0225$*		$p = 0.021$	
Complete response rate (mantle-cell lymphoma)	51%	24%	Not reported (NR)	
	HR, 1.95; $p = 0.0180$†			
Median progression-free survival (all)	NR		69.5 mo	31.2 mo
			HR, 0.58; $p < 0.0001$	
Select adverse events	**BR** (n = 224)	**R-CHOP/R-CVP** (n = 223)	**BR** (n = 261)	**R-CHOP** (n = 253)
Nausea (any grade)	63%	48%	NR	NR
Fatigue (any grade)	51%	50%	NR	NR
Alopecia (any grade)	NR	NR	0%	100%
Neutropenia (Grade 3 or 4)	44%	70%	29%	69%
Lymphopenia (Grade 3 or 4)	62%	30%	74%	43%
Leukopenia (Grade 3 or 4)	38%	54%	37%	72%

* Test for noninferiority; † Test for superiority

HR = hazard ratio

[1] Flinn IW et al. *Proc ICML* 2013;**Abstract 084**; [2] Rummel MJ et al. *Lancet* 2013;381(9873):1203-10.

R-CHOP in terms of overall response rate and complete response rate in low-grade lymphomas, although in the STiL trial complete response rates were better with BR. The slight difference in the use of R-CVP or R-CHOP in the design of the BRIGHT trial may explain the slightly lower rate of complete responses observed. The preliminary BRIGHT results suggest that BR is noninferior to R-CHOP or R-CVP.

In my practice BR is generally better tolerated than R-CHOP — no question about it. Most of my patients receiving BR are young parents who are able to work full time. Unlike R-CHOP, not much toxicity occurs with BR. ■

SELECT PUBLICATIONS

Flinn IW et al. **An open-label, randomized study of bendamustine and rituximab (BR) compared with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in first-line treatment of patients with advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL): The Bright study.** *Proc ASH* 2012;**Abstract 902**.

Fowler N et al. **Lenalidomide and rituximab for untreated indolent lymphoma: Final results of a phase II study.** *Proc ASH* 2012;**Abstract 901**.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial.** *Lancet* 2013;381(9873):1203-10.

Rummel MJ et al. **Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas — Final results of the randomized Phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2010;**Abstract 856**.