INTERVIEW

## Joseph M Connors, MD

Dr Connors is Clinical Director at BC Cancer Agency Centre for Lymphoid Cancer and Clinical Professor at the University of British Columbia in Vancouver, British Columbia, Canada.

### Tracks 1-14



## Select Excerpts from the Interview

### Tracks 3-4

**DR LOVE:** What are your thoughts on the data evaluating bendamustine/rituximab (BR) for previously untreated indolent or MCL, particularly the results from the StiL NHL 1-2003 trial that were recently published and the more recent BRIGHT study?

**DR CONNORS:** Bendamustine has had a peculiar development path, originally being developed and used behind the "Iron Curtain" and then gradually moving into the Western world. The first study you mentioned was a comparison of R-CHOP to BR, and somewhat to everyone's surprise the BR combination outperformed R-CHOP.

**4.1** **Phase III Study Results with Bendamustine/Rituximab (BR) versus Standard First-Line Therapy for Indolent Non-Hodgkin Lymphoma and Mantle-Cell Lymphomas**

| | BRIGHT[1] | | StiL NHL 1-2003[2] | |
|---|---|---|---|---|
| **Efficacy** | **BR** (n = 213) | **R-CHOP or 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% |
| | CR ratio = 1.26; $p = 0.0225$* | | $p = 0.021$ | |
| Complete response rate (mantle-cell lymphoma) | 51% | 24% | Not reported (NR) | |
| | CR ratio = 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 = 221) | **R-CHOP or R-CVP** (n = 215) | **BR** (n = 261) | **R-CHOP** (n = 253) |
| Nausea (any grade) | 63% | 48% | NR | NR |
| Fatigue (any grade) | 51% | 50% | NR | NR |
| Alopecia (any grade) | 4% | 34% | 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

CVP = cyclophosphamide/vincristine/prednisone; CR = complete response; HR = hazard ratio

[1] Flinn IW et al. *Proc ICML* 2013;**Abstract 084**; Flinn IW et al. *Proc ASH* 2012;**Abstract 902**.
[2] Rummel MJ et al. *Lancet* 2013;381(9873):1203-10.

Progression-free survival was substantially improved, as was tolerability, without the cardiotoxicity or the same level of myelosuppression (Rummel 2013; [4.1]).

Thus, the side-effect profile of bendamustine is more attractive. This has led to wide adoption of the BR combination for patients with indolent B-cell lymphomas. That being said, the StiL study concentrated more on efficacy, and I'm not sure we were able to discern the full spectrum of toxicity.

The BRIGHT study has now contributed some useful information about the spectrum of toxicity. It reminds us that although bendamustine is a potent agent, it does cause myelosuppression and somewhat more nausea than expected (Flinn 2013; [4.1]). In our experience here in British Columbia, we've observed more rashes with bendamustine, so the patients are definitely still experiencing chemotherapy-type symptoms. But these symptoms are all manageable, and bendamustine is attractive to older patients, who seem to be able to tolerate it fairly well in full doses.

**DR LOVE:** Do you generally use rituximab maintenance any time you're administering rituximab/chemotherapy for follicular lymphoma, or are there situations in which you don't take such an approach?

**DR CONNORS:** That practice has become our standard for patients with indolent lymphomas. Although studies that addressed its potential usefulness were focused on follicular lymphoma (FL), it doesn't seem too much of an extrapolation to include the other indolent B-cell lymphomas.

Debate continues about which maintenance schedule to use, with no clear superiority in any one of them. So you'll see variations in the dosing between 375 mg/m$^2$ and 500 mg/m$^2$, and you'll see variation in the interval between 2 months and 3 months. I suppose we're being a bit parsimonious here, but with no evidence in favor of one or the other, we use the every 3-months schedule and the 375-mg/m$^2$ dosing.

## Track 5

**DR LOVE:** A strategy that's currently being investigated in the large Phase III RELEVANCE trial is the so-called R-squared (R$^2$) regimen of lenalidomide and rituximab versus standard therapy — BR, R-CHOP or R-CVP (rituximab with cyclophosphamide/vincristine/prednisone) — followed by rituximab maintenance for patients with previously untreated FL. What are your thoughts on this study (NCT01650701)?

**DR CONNORS:** We're in the final stages of gaining approval to join that trial through the NCIC Clinical Trials Group.

Exciting preliminary data with this combination lead us to believe that it might perform as well as any other regimen we have to offer, including BR. These data point to a high level of efficacy and favorable tolerability with the R$^2$ regimen (Fowler 2012; Martin 2013; [4.2]).

The management of FL is suddenly accelerating. I believe we should look toward a day in the not-too-distant future when we won't be talking at all about regimens like CHOP or CVP. And we may well also move beyond combinations like BR.

**4.2**

### ALLIANCE/CALGB-50803: A Phase II Trial of Lenalidomide/Rituximab for Previously Untreated Follicular Lymphoma

| Response | Overall (n = 57) | Response by FLIPI score | | |
|---|---|---|---|---|
| | | FLIPI 0-1 (n = 17) | FLIPI 2 (n = 36) | FLIPI 3 (n = 2) |
| ORR | 93% | 94% | 92% | 100% |
| CR | 72% | 77% | 70% | 100% |
| PR | 21% | 18% | 22% | NR |
| SD | 4% | 0% | 6% | NR |

FLIPI = Follicular Lymphoma International Prognostic Index; ORR = overall response rate; CR = complete response; PR = partial response; NR = not reported; SD = stable disease

Martin P et al. *Proc ICML* 2013;**Abstract 063**.

## Track 7

**DR LOVE:** What is your take on the new data reported at ASCO 2013 on the efficacy of the anti-CD20 antibody obinutuzumab (GA101) in previously untreated chronic lymphocytic leukemia (CLL)?

**DR CONNORS:** It was a little complicated to figure out what was and was not comparable. The trial was structured with a standard arm of chlorambucil and then 2 separate

experimental arms — chlorambucil with obinutuzumab and chlorambucil with rituximab. So the comparisons that were reported at ASCO and examined for statistical validity were obinutuzumab and chlorambucil to chlorambucil alone and then separately rituximab and chlorambucil to chlorambucil alone.

The authors purposely avoided comparing the 2 experimental arms, so we were left to imagine the comparison. I am a little wary of that because differences exist in the distribution of prognostic factors and other aspects of the patient groups on each of these arms. The study must mature further before we can make those comparisons.

That said, it did emerge that on a backbone of chlorambucil you can improve outcomes with either of the 2 anti-CD20 interventions (Goede 2013; [4.3]). Some theoretical and preclinical reasoning supports the possible superiority of obinutuzumab, but enough similarity is evident between the 2 antibodies that I want to see more hard data and firm evidence before I'm willing to believe that obinutuzumab is a more effective agent.

I don't believe we will see obinutuzumab on the market and commercially available until it demonstrates at least equivalence if not superiority to another anti-CD20 molecule.

Editor's note: Subsequent to this interview additional important findings from this study were reported in a press release (4.3), and on November 1, 2013, the FDA granted approval of obinutuzumab in combination with chlorambucil for previously untreated CLL. ■

**4.3**

**Results from the Phase III CLL11 Trial of Obinutuzumab (GA101) with Chlorambucil (Clb) or Rituximab (R) with Clb versus Clb Alone in Previously Untreated Chronic Lymphocytic Leukemia**

| | Stage Ia | | Stage Ib | |
|---|---|---|---|---|
| **Efficacy**[1] | **GA101 + Clb** | **Clb** | **R + Clb** | **Clb** |
| **Overall response rate** (n = 212, 106, 217, 110) | 75.5% | 30.2% | 65.9% | 30.0% |
| **Median progression-free survival** (n = 238, 118, 233, 118) | 23.0 mo | 10.9 mo | 15.7 mo | 10.8 mo |
| | HR = 0.14; $p < 0.0001$ | | HR = 0.32; $p < 0.0001$ | |

Press release (July 24, 2013): At a preplanned interim analysis, an independent data monitoring committee determined that the study met its primary endpoint, showing that GA101 with chlorambucil helped people live significantly longer without their disease worsening (progression-free survival) compared to rituximab with chlorambucil. Final data from the CLL11 study will be submitted to the American Society of Hematology's 55th Annual Meeting in December 2013.[2]

[1] Goede V et al. *Proc ASCO* 2013;**Abstract 7004**; [2] Available at: **http://www.roche.com/media/media_releases/med-cor-2013-07-24.htm**.

## SELECT PUBLICATIONS


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

Goede V et al. **Obinutuzumab (GA101) + chlorambucil (Clb) or rituximab (R) + Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase 3 trial.** *Proc ASCO* 2013;**Abstract 7004**.

Martin P et al. **Alliance/CALGB 50803: A phase 2 trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma.** *Proc ICML* 2013;**Abstract 063**.