INTERVIEW

Steven Coutre, MD

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Tracks 1-12

Track 1 CLL10: Results of a Phase III trial of fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR) for patients with previously untreated advanced chronic lymphocytic leukemia (CLL)

Track 2 Activity and tolerability of obinutuzumab and chlorambucil versus rituximab and chlorambucil for older patients with previously untreated CLL and comorbidities

Track 3 Management of obinutuzumab-associated infusion reactions

Track 4 Use of single-agent obinutuzumab for previously untreated CLL

Track 5 Integrating ibrutinib into the CLL treatment algorithm for patients with and without adverse cytogenetics

Track 6 Bleeding risk and use of anticoagulants in patients receiving ibrutinib

Track 7 Management of atrial fibrillation in patients receiving ibrutinib

Track 8 Clinical experience with idelalisib in combination with rituximab for relapsed CLL

Track 9 Sequencing of ibrutinib and idelalisib in CLL

Track 10 Activity and incidence of tumor lysis syndrome with the novel second-generation Bcl-2 inhibitor venetoclax (ABT-199) in CLL

Track 11 Arsenic trioxide and ATRA in the treatment of acute promyelocytic leukemia

Track 12 Activity of the bispecific T-cell engager blinatumomab in Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: Would you discuss the results of the Phase III CLL10 trial of fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR) for patients with untreated advanced chronic lymphocytic leukemia (CLL) (Eichhorst 2014)?

DR COUTRE: FCR has become the major regimen used for initial treatment of CLL in fit patients, but BR is becoming increasingly popular and has a reputation for being a kinder and gentler regimen. The CLL10 trial of FCR versus BR included patients older and younger than age 65. The primary endpoint was progression-free survival (PFS), and FCR was superior. More patients achieved a complete response with FCR, and that translated to a PFS of 55.2 months versus 41.7 months with BR.

The tradeoff was tolerability. FCR led to a higher incidence of neutropenia, thrombocytopenia and infections. By age group, the tolerability issues were observed primarily

in patients older than age 65. However, there is no cutoff age in place for the use of FCR. The most important aspect is the treatment goal. One has to consider each patient individually, and one size does not fit all.

DR LOVE: How have the results of the German Phase III CLL11 trial of chlorambucil with or without the anti-CD20 monoclonal antibodies obinutuzumab or rituximab for patients with untreated CLL and comorbidities influenced your practice?

DR COUTRE: The relevant part of the CLL11 trial was the comparison of obinutuzumab/chlorambucil to rituximab/chlorambucil (Goede 2014). In terms of the primary endpoint of PFS, the obinutuzumab/chlorambucil combination was superior at 26.7 months versus 15.2 months for rituximab/chlorambucil. No difference is apparent yet in overall survival (OS). If you're considering rituximab, you might opt for obinutuzumab instead because patients achieve better and more durable responses. In my practice, I would choose obinutuzumab for an older, symptomatic patient for whom I want to achieve disease control if I didn't feel that the patient would tolerate BR.

In the trial, obinutuzumab was used in combination with chlorambucil. However, I do not believe that chlorambucil adds any benefit to obinutuzumab, and therefore I always administer obinutuzumab as a single agent rather than in combination with chlorambucil even for older patients.

Tracks 5, 7-10

DR LOVE: What is your clinical experience with ibrutinib, and how do you integrate it into the treatment algorithm for patients with CLL with and without adverse cytogenetics?

DR COUTRE: Ibrutinib has tremendous activity. Essentially all patients respond to ibrutinib therapy when it is initially administered, including those who often do not respond to the standard agents, such as patients with the 17p deletion or those with fludarabine-refractory disease. It is great to know that you can tell your patients that you are going to recommend a once-a-day pill and they're going to experience a response.

With ibrutinib, the lymph nodes shrink dramatically in a matter of days and at the same time, you see lymphocytosis. Fortunately, that doesn't cause any clinical problems, but you need to make your patients aware of this issue. Ibrutinib is generally quite well tolerated. It causes easy bruising and a bit of diarrhea, which eventually goes away. I have patients who've been on ibrutinib continuously for up to 5 years. It is not associated with cumulative side effects. As a result, ibrutinib is FDA approved for patients with CLL who have received 1 prior therapy. It is also indicated up front for patients with 17p deletion.

DR LOVE: Would you administer ibrutinib up front for patients without 17p deletion?

DR COUTRE: Absolutely. We've recently reported data from the randomized Phase III RESONATE-2 trial addressing that issue in patients with treatment-naïve disease. Patients aged 65 or older with untreated CLL or small lymphocytic lymphoma (SLL) without 17p deletion received chlorambucil or ibrutinib, and single-agent ibrutinib was superior (Tedeschi 2015; [1.1]).

The RESONATE-2 trial also revealed that ibrutinib can cause atrial fibrillation. However, it was generally brief in duration, occurring only for a matter of days. We

1.1

RESONATE-2: Efficacy and Safety Results from a Phase III Trial of Ibrutinib (Ibr) versus Chlorambucil (Clb) for Patients Age 65 or Older with Untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma without 17p Deletion

Efficacy (by IRC)	Ibr	Clb	HR	*p*-value
Median PFS*	NR	18.9 mo	0.16	<0.0001
Median OS	NR	NR	0.16	0.0010
24-month OS	97.8%	85.3%	—	—
Median EFS	NR	12 mo	0.17	<0.0001
ORR	86.0%	35.3%	—	—
CR/CRi	4.4%	1.5%	—	—
≥50% reduction in LNB	91.2%	36.8%	—	<0.0001
Select AEs (all grades)	**Ibr**		**Clb**	
Leading to discontinuation	9%		23%	
Atrial fibrillation	6%		1%	
Major hemorrhage	4%		2%	

IRC = independent review committee; HR = hazard ratio; PFS = progression-free survival; NR = not reached; OS = overall survival; EFS = event-free survival; ORR = overall response rate; CR = complete response; CRi = incomplete CR; LNB = lymph node burden; AEs = adverse events

* Consistent across subgroups, including ≥70 years, del(11q) and unmutated IGHV

- Rates of sustained hematologic improvements were significantly higher with Ibr versus Clb, including for patients with baseline anemia (84% versus 45%; $p < 0.0001$) or thrombocytopenia (77% versus 43%; $p = 0.0054$).
- Median duration of treatment was 17.4 mo with Ibr versus 7.1 mo with Clb.
- Hypertension was more frequent with Ibr but limited to Grade ≤3.

Tedeschi A et al. *Proc ASH* 2015;**Abstract 495**.

need to understand it better, but for right now, I would say it shouldn't preclude you from choosing ibrutinib for patients with even chronic atrial fibrillation if you feel it's the best agent to treat their CLL.

DR LOVE: How do idelalisib and ibrutinib "match up" in relapsed CLL, and how do you approach sequencing these agents?

DR COUTRE: Idelalisib is an effective agent. In our early trials of single-agent idelalisib, I couldn't tell you if its efficacy was any different from that of ibrutinib. The pattern of response is exactly the same, with rapid shrinkage of lymph nodes and lymphocytosis that resolves with time. However, the safety issues are different. Idelalisib does not cause bleeding issues or atrial fibrillation, but many patients may experience asymptomatic transaminitis. When this happens, idelalisib should be discontinued. The transaminitis usually resolves within a couple of weeks, after which idelalisib can be reinitiated. Most often, even without dose reduction, it never reoccurs.

As patients stay on the drug longer, we have also observed a diarrheal illness. The median time to its onset is about 9 months, although it can present up to 2 or 3 years after initiation of treatment. It appears as profuse, watery diarrhea, with all the characteristics of colitis. We've learned to treat it with steroids.

Outside of a trial setting, I'll choose either idelalisib or ibrutinib for patients with previously treated disease. Although I will not administer BR to a patient who received

first-line FCR, I will consider idelalisib or ibrutinib as second-line therapy. I tend to use ibrutinib to avoid idelalisib-associated colitis. We have limited experience with idelalisib after progression on ibrutinib or vice versa, but patients can respond.

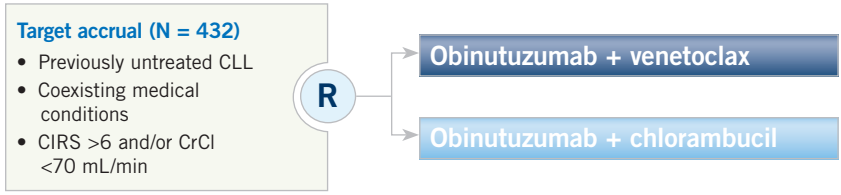
DR LOVE: What are your thoughts on the investigation of the novel second-generation Bcl-2 inhibitor venetoclax in CLL?

DR COUTRE: In a Phase I dose-escalation trial, venetoclax produced extremely high response rates, including among patients with heavily pretreated disease (Seymour 2013). However, it is associated with tumor lysis syndrome, but we have learned that a reduced initial dose followed by slow dose escalation decreases the likelihood of this toxicity. Several trials of venetoclax in CLL are ongoing, including the Phase III CLL14 trial evaluating obinutuzumab in combination with venetoclax or chlorambucil for patients with previously untreated CLL and coexisting comorbidities (1.2). ■

1.2

CLL14: A Phase III Trial of Obinutuzumab in Combination with Venetoclax or Chlorambucil for Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Coexisting Comorbidities

Protocol ID: NCT02242942



CIRS = cumulative illness rating scale; CrCl = creatinine clearance

- Prior to the randomized study, CLL14 includes a nonrandomized safety run-in phase to assess the tolerability of obinutuzumab and venetoclax
- **Primary endpoint:** Progression-free survival

Fischer K et al. *Proc ASH* 2015;**Abstract 496**; **www.clinicaltrials.gov**. Accessed December 2015.

SELECT PUBLICATIONS

Eichhorst B et al. **Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 study).** *Proc ASH* 2014;**Abstract 19**.

Fischer K et al. **Results of the safety run-in phase of CLL14 (BO25323): A prospective, open-label, multicenter randomized phase III trial to compare the efficacy and safety of obinutuzumab and venetoclax (GDC-0199/ABT-199) with obinutuzumab and chlorambucil in patients with previously untreated CLL and coexisting medical conditions.** *Proc ASH* 2015;**Abstract 496**.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.

Seymour JF et al. **Bcl-2 inhibitor ABT-199 (GDC-0199) monotherapy shows anti-tumor activity including complete remissions in high-risk relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).** *Proc ASH* 2013;**Abstract 872**.

Tedeschi A et al. **Results from the international, randomized phase 3 study of ibrutinib versus chlorambucil in patients 65 years and older with treatment-naïve CLL/SLL (RESONATE-2).** *Proc ASH* 2015;**Abstract 495**.