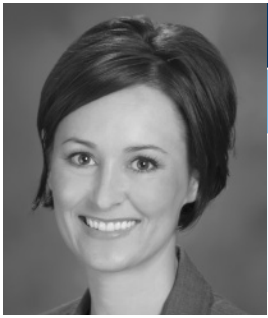


INTERVIEW

Loretta J Nastoupil, MD

Dr Nastoupil is Assistant Professor in the Department of Lymphoma/Myeloma in the Division of Cancer Medicine and Director of the Lymphoma Outcomes Database at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What are some of the factors that you take into account when considering a patient for CAR T-cell therapy?

DR NASTOUPIL: We generally like to have some sense of response in patients before administering CAR-T therapy. If I can initially debulk some of the tumor burden, I believe they will have a better outcome. This has not been described in prospective studies, but we do know that CAR-T therapies are generally associated with fairly high toxicity. So if we can have some idea that the patient will respond to an immune therapy approach with an agent such as lenalidomide, and if I can reduce the proliferative rate prior to proceeding with CAR-T therapy, I'm much more optimistic about the outcome.

The efficacy of CAR-T therapy appears to be quite high, but some patients do not benefit, and we're trying to understand why. We're observing efficacy rates of more than 60% and CR rates of more than 50%, which is quite striking. So this is an all-or-

none type of approach in which we're aiming for a CR, and we believe those CRs to be durable.

We know that the toxicity should not be discounted, and it should be managed with a multidisciplinary approach in centers with access to ICU care because these patients can become quite sick in a short time. My general opinion is that CAR-T therapy is more toxic than ASCT, but it might be applicable when a patient with chemorefractory disease is not a candidate for ASCT or an allogeneic transplant.

Some of the toxicities that have been observed are cytokine release syndrome, fever, neurotoxicity, confusion and cerebral edema. Seizure activity is not infrequent. Generally, these events have all been reversible, but the cerebral edema is what we worry about the most.

DR LOVE: What exactly are "off-the-shelf" CAR T cells?

DR NASTOUPIL: You identify an antigen for which a T cell is already prepared and sitting on a shelf, meaning someone else's T cell that will bind and effectively eliminate that antigen. An ASH 2015 presentation from Dr Helen Heslop's group evaluated these off-the-shelf CAR T cells and reported high response rates (Omer 2015). The efficacy in terms of duration of response is still an unanswered question, but this approach appears quite appealing.

DR LOVE: Is it likely that one of these therapies will be approved soon, and in what disease?

DR NASTOUPIL: None of these are currently FDA approved, but studies of CAR-T therapies are much further along in the acute leukemias than in the lymphomas, although we are accumulating data with DLBCL. We've completed a study that we expect will be considered by the FDA in the spring of 2017.

I have a handful of patients who I know would no longer be with us if they did not have access to this therapy. I do believe that this will continue to be investigated and continue to evolve. If we can reduce the toxicity while maintaining the efficacy, this will be *really* exciting.

Tracks 5-6

DR LOVE: What is your take on the activity and tolerability of the BTK inhibitors ibrutinib and acalabrutinib in CLL?

DR NASTOUPIL: We know that ibrutinib performs well in relapsed CLL in terms of high response rates, and we know of some off-target effects with ibrutinib and that it's not purely selective for inhibiting BTK. What is the impact of those off-target effects? We know they probably add to the toxicity, including platelet aggregation, rash and diarrhea. One of the interests in pursuing more selective agents such as acalabrutinib is the impact on efficacy. And can we reduce some of the toxicity?

The overall response rate with acalabrutinib was 95% (Byrd 2016). About 30% of patients harbored a 17p deletion, and 100% of those patients experienced a response. Most of the responses will be partial responses or partial responses with persistent leukocytosis. But for patients with relapsed CLL, is that a failure? I don't believe so if you can gain adequate disease control for long periods.

We are learning more about acalabrutinib as time goes on. We do know from the *New England Journal* paper that no major bleeding events were reported with this agent (Byrd 2016; [4.1]). What we don't know is, over time, will that story change? Acalabrutinib appears to be more potent, and perhaps we can intensify the dosing because we're seeing fewer side effects.

4.1

ACE-CL-001 Trial: A Novel Bruton Tyrosine Kinase Inhibitor, Acalabrutinib, for Chronic Lymphocytic Leukemia

	Overall response rate	Partial response (PR) rate	PR with lymphocytosis
All evaluable patients (n = 60)	95%	85%	10%
Del(17p13.1) (n = 18)	100%	89%	11%
Prior idelalisib (n = 4)	100%	75%	25%
Adverse events (n = 61)	**Grades 1 and 2**		**Grades 3 and 4**
Headache	43%		0%
Diarrhea	38%		2%
Pyrexia	20%		3%
Upper respiratory tract infection	23%		0%

- No cases of major bleeding or atrial fibrillation at 14.3 months follow-up

Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

Tracks 11-12

DR LOVE: What is the design and status of the ongoing Phase III RELEVANCE study?

DR NASTOUPIL: RELEVANCE is a large, international, multicenter Phase III study for which all patients must have high tumor burden to be eligible. These are patients who you typically think of as needing chemoimmunotherapy. The study is a head-to-head comparison of R-CHOP, BR or R-CVP to lenalidomide/rituximab (R^2) as front-line therapy for FL (4.2).

The dosing strategy includes more intensive lenalidomide until the patient achieves a CR, which is typically assessed around 6 months. Patients can then change to maintenance lenalidomide, which is a lower dose, for 18 months duration of lenalidomide therapy. Patients also receive up to 30 months of rituximab therapy, including 24 months of maintenance, similar to the approach we use after front-line chemoimmunotherapy. The primary study endpoint is PFS. Enrollment was completed some time ago, and we're waiting to hear the study results.

DR LOVE: If the study ended up showing equivalent efficacy, would you choose R^2 because of tolerability?

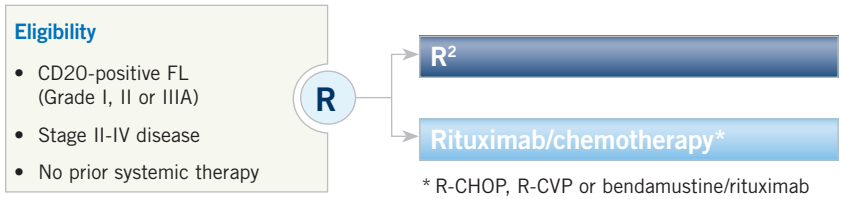
DR NASTOUPIL: I used to at least pitch to patients that this was a nonchemotherapy approach and thus would be well tolerated. But lenalidomide and rituximab have fairly high incidences of fatigue, myalgias, fever and cytopenias. It's not infrequent to have Grade 3 or 4 neutropenia.

4.2

RELEVANCE: A Phase III Study Comparing Lenalidomide with Rituximab (R^2) to Rituximab/Chemotherapy for Previously Untreated Follicular Lymphoma (FL)

Protocol ID: NCT01650701

Target Accrual: 1,031 (Closed)



* R-CHOP, R-CVP or bendamustine/rituximab

www.clinicaltrials.gov. Accessed March 2017.

What's striking about R^2, at least in our experience, is that the side-effect intensity seems to be higher in the first few months and then tends to stabilize or improve over time. It's unclear whether patients become accustomed to the side-effect profile and don't report it or don't seem to be bothered by it or whether it becomes easier over time. But the first 2 months of R^2 are not a "free lunch."

We don't know whether patients who have highly proliferative tumors or a high tumor burden need chemotherapy in that setting rather than R^2. We generally do see slower time to response with the immune therapy approaches than we do with chemotherapy. Hopefully, that question will be answered with this study.

DR LOVE: What did your group report in the recent paper you published on characteristics and management of rash after treatment with R^2 in patients with previously untreated indolent NHL (Fowler 2015)?

DR NASTOUPIL: We wanted to describe our experiences with this combination because we've seen quite a few patients for whom lenalidomide was stopped because of rash. We've learned that a rash is not uncommon and is frequently Grade 3, meaning a large amount of the body surface area is affected. It's typically a red, sometimes pruritic rash. The most striking characteristic is that if you stop the lenalidomide, the rash almost always goes away.

So we wanted to reassure community doctors that an uncomfortable, full-body rash is not uncommon among patients receiving R^2. You can treat it with antihistamines and a short course of low-dose steroids if you want to get rid of it faster, but generally speaking, we are not altering therapy because of this rash. This phenomenon can be managed with a drug holiday if need be, and then the patient can be rechallenged, even those patients who have experienced Grade 3 rash. ■

SELECT PUBLICATIONS

Byrd JC et al. **Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia.** *N Engl J Med* 2016;374(4):323-32.

Byrd JC et al; RESONATE Investigators. **Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.** *N Engl J Med* 2014;371(3):213-23.

Fowler NH et al. **Characteristics and management of rash following lenalidomide and rituximab in patients with untreated indolent non-Hodgkin lymphoma.** *Haematologica* 2015;100(11):e454-7.

Omer B et al. **Administration of most closely HLA-matched multivirus-specific T cells for the treatment of EBV, CMV, AdV, HHV6, and BKV post allogeneic hematopoietic stem cell transplant.** *Proc ASH* 2015;**Abstract 622**.