INTERVIEW

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Track 3 SWOG-S0016: Results from a Phase III study of R-CHOP versus CHOP in combination with ^{131}I-tositumomab for patients with newly diagnosed FL

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Track 16 Proposed study of ABVD versus AVD in combination with brentuximab vedotin in advanced-stage HL

Track 17 **Case discussion:** An 80-year-old man with CD5-positive, CD23-negative, t(11;14) translocated MCL receives 6 cycles of rituximab/bendamustine and is now considering rituximab maintenance

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you comment on the data from the RESORT trial recently presented at ASH 2011?

DR FRIEDBERG: The RESORT trial evaluated patients with low tumor burden indolent lymphoma. Patients who did not require treatment by formal criteria received

4 weekly doses of rituximab. Responding patients were then randomly assigned to 2 therapy approaches — rituximab maintenance continuously once every 3 months until progression or rituximab weekly times 4 at disease progression. The primary study endpoint was time to failure of rituximab. The presentation at ASH was limited to the subgroup of patients with follicular lymphoma (FL).

Both groups had reasonably long progression-free survival (PFS), and no difference was seen in time to failure of rituximab with the 2 different dosing strategies (Kahl 2011). The ECOG group concluded that both strategies were active but more rituximab was administered in the maintenance arm with slightly more toxicity, so they favored the scheduled re-treatment approach rather than the maintenance approach.

These findings affect my practice because it's challenging to interpret RESORT and reconcile those data with the SAKK results. The SAKK-35/98 study was conducted in 1998, but the 10-year follow-up results are now available. This study enrolled patients with a variety of histologies of both newly diagnosed and rituximab-naïve, relapsed lymphoma. The study evaluated 2 schedules of rituximab — weekly times 4 versus weekly times 4 followed by 4 doses of rituximab 2 months apart. Some people consider that maintenance, and others consider it an extended schedule. It's really 8 doses of rituximab versus 4 doses of rituximab.

For patients with FL, the preliminary results published in 2004 reported a doubling in time to progression for those who received 8 doses of rituximab, and that benefit was durable at 10 years of follow-up (Martinelli 2010; [3.1]). Of patients with newly diagnosed disease who received 8 doses of rituximab, 45% have not experienced progression. A borderline survival advantage was observed in the patients who received 8 doses versus 4 doses of rituximab.

Those results were hypothesis generating for me and suggest that if you're using single-agent rituximab, administering it on a more prolonged schedule may provide further durability. That approach wasn't formally studied in the RESORT trial, but I believe it does suggest some benefit to the extended schedule. In my practice, if I'm administering single-agent rituximab to a patient, I use the SAKK schedule of 8 doses, and I don't feel at all concerned that administering additional maintenance rituximab makes a difference based on the RESORT results.

3.1

SAKK-35/98 Study: Long-Term Follow-Up of Prolonged versus Short-Course Rituximab for Patients with Follicular Lymphoma

	Short-course rituximab (n = 78)	Prolonged rituximab (n = 73)	*p*-value
Median event-free survival (EFS)	13 months	24 months	<0.001
EFS*, all patients			
At 5 years	13%	27%	
At 8 years	5%	27%	—
EFS in chemotherapy-naïve patients (n = 38)			
At 8 years	22%	45%	0.045

* EFS: Time until progression, relapse, second tumor or death

Martinelli G et al. *J Clin Oncol* 2010;28(29):4480-4.

Tracks 3, 5

DR LOVE: Would you discuss the results your group presented at ASH 2011 on R-CHOP versus CHOP in combination with ^{131}I-tositumomab for patients with newly diagnosed FL?

DR FRIEDBERG: The SWOG-S0016 trial initially randomly assigned patients to 3 arms — CHOP alone, R-CHOP or CHOP followed by ^{131}I-tositumomab. After the first year when data became available that R-CHOP was better than CHOP, the CHOP alone arm was dropped, making this trial a head-to-head comparison of R-CHOP versus CHOP followed by ^{131}I-tositumomab. One important conclusion is that both arms performed better than we anticipated when we designed the study.

That having been said, no difference was observed between the 2 arms with regard to PFS or overall survival. Some mild toxicity differences occurred, as would be expected — slightly higher neutropenia in the group who received rituximab and some hypothyroidism in patients who received radioimmunotherapy (RIT). Some cases of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and toxic deaths occurred on the RIT arm (Press 2011; [3.2]). For people who were hoping that up-front RIT would provide a benefit, this was disappointing.

Another important study that evaluated RIT was the FIT trial, in which patients were randomly assigned to ibritumomab tiuxetan consolidation versus observation. The patients who received RIT consolidation experienced prolonged PFS. Longer-term follow-up of that study presented at ASH 2010 suggested increased numbers of MDS and AML in the patients who received ibritumomab tiuxetan (Hagenbeek 2010; [3.3]).

3.2

SWOG-S0016: A Phase III Study of R-CHOP versus CHOP Followed by ^{131}I-Tositumomab for Patients with Newly Diagnosed Follicular Lymphoma

	R-CHOP	CHOP → ^{131}I-tositumomab	*p*-value
Overall response rate (n = 264, 260)	85%	86%	0.90
Two-year PFS (n = 267, 265)	76%	80%	0.11
Two-year overall survival (n = 267, 265)	97%	93%	0.08
Treatment-related mortality (n = 263, 263)	0.4%	1.5%	0.37
AML/MDS (n = 267, 265)	1.1%	2.7%	0.34

PFS = progression-free survival; AML = acute myeloid leukemia; MDS = myelodysplastic syndromes

Press OW et al. *Proc ASH* 2011;**Abstract 98**.

Tracks 8-9

DR LOVE: What are your thoughts on the novel agent obinutuzumab (GA101) under investigation in non-Hodgkin lymphoma (NHL)?

DR FRIEDBERG: A preliminary analysis we presented at ASH 2011 was designed to compare the third-generation anti-CD20 monoclonal antibody obinutuzumab to rituximab head to head in patients with rituximab-sensitive, relapsed NHL. The primary

3.3

FIT: A Phase III Trial of Consolidation Therapy with Yttrium-90 Ibritumomab Tiuxetan After First Remission in Advanced Follicular Lymphoma

	Ibritumomab tiuxetan (n = 207)	No additional therapy (n = 202)	Hazard ratio	*p*-value
Median progression-free survival (PFS)	49 mo	14 mo	NR	NR
Five-year PFS	47%	29%	0.51	<0.0001
Secondary cancer Cases of MDS/AML	7.7% 2.9%	4.5% 0.5%	— —	0.19 0.063

Median follow-up = 66.2 months (5.5 years)
MDS = myelodysplastic syndrome; AML = acute myeloid leukemia

Hagenbeek A et al. *Proc ASH* 2010;**Abstract 594**.

endpoint of the study was response rate, and obinutuzumab produced a higher response rate than did rituximab (Sehn 2011; [3.4]).

However, essentially no difference in PFS was noted between the 2 study arms. Despite the disappointing PFS result, 3 large randomized Phase III trials are under way to determine whether this agent can beat rituximab. These studies are being performed in up-front FL, relapsed FL and up-front diffuse large B-cell lymphoma with a bold international goal of enrolling more than 2,000 patients.

3.4

GAUSS Study: Preliminary Analysis* of a Phase II Trial of Obinutuzumab (GA101) versus Rituximab for Patients with Relapsed CD20-Positive Indolent B-Cell Non-Hodgkin Lymphoma

	Obinutuzumab (n = 74)	Rituximab (n = 75)
Overall response rate (by investigator assessment)	43.2%	38.7%
Progression-free survival	79.7%	82.7%

* Primary efficacy analysis conducted after induction in patient population with FL

Sehn LH et al. *Proc ASH* 2011;**Abstract 269**.

Tracks 11, 15-16

DR LOVE: Would you talk about what's been reported recently with brentuximab vedotin and what new directions we're heading in with this agent?

DR FRIEDBERG: I was involved in the pivotal study of brentuximab vedotin and I've seen many patients with no other therapeutic options who were approaching hospice care have remarkable turnaround in their performance status and impressive durability of response with this agent (3.5).

When you have an active single agent that probably has the highest response rate in relapsed Hodgkin lymphoma, you want to try to move it up front so more patients can benefit. A study reported at ASH 2011 evaluated the addition of brentuximab vedotin to the ABVD regimen for patients with newly diagnosed advanced-stage Hodgkin lymphoma. The authors reported increased pulmonary toxicity that they felt

3.5

Response and Maximum Tumor Reduction with Brentuximab Vedotin in Relapsed or Refractory Hodgkin Lymphoma (HL) and Systemic Anaplastic Large Cell Lymphoma (sALCL)*

	HL[1] (n = 102)	sALCL[2] (n = 58)
Overall response rate	75%	86%
Complete remission	34%	53%
Maximum tumor reduction (n = 96, 57)	94%	97%

* By independent review facility

[1] Younes A et al. *J Clin Oncol* 2012;[Epub ahead of print].
[2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

was secondary to the combination of bleomycin and brentuximab vedotin. The rate of pulmonary toxicity was as high as 40%. They elected to drop bleomycin and continue with brentuximab vedotin and AVD.

Patients who received AVD in combination with brentuximab vedotin did not exhibit pulmonary toxicity. For a single-arm study the response rate was high, suggesting that this is an approach that could move forward in a randomized trial (Younes 2011; [3.6]). A proposed global randomized study will evaluate ABVD versus AVD in combination with brentuximab vedotin, and the cooperative groups in the United States are in final stages of discussions planning our next Intergroup study in advanced-stage Hodgkin lymphoma. I am certain that brentuximab vedotin will be part of that study too. ■

3.6

Front-Line Therapy with Brentuximab Vedotin (B-Vedotin) and ABVD or AVD for Patients with Newly Diagnosed Advanced-Stage Hodgkin Lymphoma

	ABVD + B-vedotin* (n = 25)	AVD + B-vedotin (n = 19)
Complete response	60%	Not yet reported
Pulmonary toxicity	40%	0%

* Fifteen of 25 patients have completed front-line therapy and have response results.
Toxicity resembling that of bleomycin alone led to its discontinuation in 10 patients. Seven of 10 continued treatment with AVD and brentuximab vedotin.
A = doxorubicin; B = bleomycin; V = vinblastine; D = dacarbazine

Younes A et al. *Proc ASH* 2011;**Abstract 955**.

SELECT PUBLICATIONS

Hagenbeek A et al. **90Y-ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-Hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, Phase III First-Line Indolent Trial (FIT) in 414 patients.** *Proc ASH* 2010;**Abstract 594**.

Kahl BS et al. **Results of Eastern Cooperative Oncology Group protocol E4402 (RESORT): A randomized Phase III study comparing two different rituximab dosing strategies for low tumor burden follicular lymphoma.** *Proc ASH* 2011;**Abstract LBA-6**.

Martinelli G et al. **Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98.** *J Clin Oncol* 2010;28(29):4480-4.

Sehn LH et al. **Randomized Phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: Preliminary analysis of the GAUSS study.** *Proc ASH* 2011;**Abstract 269**.