Expert Perspective on ASH 2014: Lymphoma

Myron S. Czuczman, MD

Abstract

The 2014 Annual Meeting and Exposition of the American Society of Hematology included many updates of previously presented studies, as well as data on different therapeutics and novel targeted agents. This perspective highlights some of the key findings in lymphoma.

Key words: Lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, T cell lymphoma, chronic lymphocytic lymphoma

The latest Annual Meeting and Exposition of the American Society of Hematology (ASH), held from December 6-9, 2014, in San Francisco, included many updates on studies that we had received preliminary data on in the past, as well as additional information on different therapeutics, including interesting data on some of the novel targeted agents. Presented here are some of the lymphoma findings from the conference, arranged by malignancy subtype. (The February issue of *The American Journal of Hematology/Oncology* will feature an update on leukemia abstracts presented at ASH.)

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of lymphoma with 2 subtypes—germinal-center B cell (GCB) and non-GCB, or activated B cell (ABC), depending on whether the determination is made by immunohistochemistry or gene expression, respectively.. We already know that lenalidomide has demonstrated activity in DLBCL. A retrospective analysis showed that patients with the non-GCB subtype appeared to have a better response to lenalidomide monotherapy compared with patients with the GCB subtype.[1] Therefore, a prospective, phase 2/3, multicenter, randomized study was initiated to compare the efficacy and safety of lenalidomide as a single agent versus investigator's choice (gemcitabine, rituximab, etoposide, or oxaliplatin monotherapy) in relapsed/refractory DLBCL (study DLC-001).[2]

With 25 patients in each major subgroup (GCB or non-GCB) either receiving lenalidomide or investigator's choice, the most pronounced clinical benefit was observed in patients with the ABC subtype with single-agent lenalidomide. Unfortunately, the lenalidomide activity was just short of what we wanted to see in order to proceed with clinical development, and so this trial did not proceed from phase 2 to phase 3. What this showed, however, was that there is a signal for improvement in the relapsed setting with lenalidomide in the ABC phenotype.[2] Also, perhaps in the future, lenalidomide combined with other agents that are active in relapsed/refractory ABC DLBCL will be evaluated to determine if the combinations will result in improved therapeutic outcomes. In addition, lenalidomide is currently being studied prospectively in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in several trials in patients with ABC DLBCL in the upfront setting.

Even though CD30 is the target for brentuximab vedotin (SGN-35), past data have shown that the drug may be active in some patients despite undetectable surface CD30 expression (as measured by immunohistochemistry).[3] Preliminary results from a phase 2 trial of brentuximab vedotin monotherapy for patients with DLBCL with undetectable CD30 were also reported. One dose of brentuximab vedotin was administered every 3 weeks until progression or intolerability. Of the 51 patients enrolled, the overall response rate (ORR) was 31%, including 10% of patients who achieved complete response (CR). Unfortunately though, the median duration of response (DOR) was only 1.9 months, and the median progression-free survival (PFS) was only 1.4 months. There were no new toxicity data compared with previous historical results.[4] Despite some activity, as a single agent it is limited based on these data, and so studies are currently being planned in CD30+ DLBCL utilizing brentuximab vedotin with other agents to improve antitumor activity.

In order to determine whether changing the CD20 antibody could benefit patients receiving salvage therapy, a randomized phase 3 study of ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed/refractory DLBCL was performed in Europe. A total of 447 autologous stem cell transplant–eligible patients were randomized: 222 to ofatumumab (O)-DHAP (cisplatin, cytarabine, dexamethasone) and 225 to rituximab (R)-DHAP, in an attempt to improve PFS and outcomes after autologous stem cell transplant. Notably, no difference in efficacy was found between the ofatumumab or rituximab arms when combined with DHAP.[5]

Even though activity was described in these 3 abstracts in relapsed/refractory DLBCL, we still need to find either novel

agents or novel combinations that will help us improve outcomes in this patient population (especially in patients not cured with upfront therapy).

Follicular Lymphoma

Recent data demonstrated significant activity of the combination of lenalidomide plus rituximab in patients with relapsed/refractory or newly diagnosed follicular indolent lymphoma (FL). In a European study in patients with untreated FL who were in need of therapy, 154 patients were randomized to rituximab alone (typical dose and schedule) or to rituximab plus lenalidomide (R^2), which was administered at 15 mg/day for a total of 19 weeks. The ORR in the combination arm was 81% versus just 61% in the rituximab-alone arm. The CR rate in the combination group was 36% compared with only 25% with rituximab monotherapy, which was highly statistically significant.[6] Further follow-up will be needed because it is still early, but these findings support previous data showing that this combination is quite effective in patients with either FL or indolent lymphoma.

Final results were presented from the maintenance part of the phase 1b GAUDI study of upfront/first-line obinutuzumab (GA-101) plus CHOP or bendamustine in FL. Patients were randomized to either G (obinutuzumab)-CHOP (n = 41) or G-bendamustine (n = 40). Patients who responded then received obinutuzumab 1000 mg maintenance therapy (n = 72, 36 in each arm) every 3 months for 2 years or until progression of disease. The CR rates at the end of maintenance compared with after induction appeared to improve somewhat. In addition, at the end of maintenance therapy, the CR rate in patients who received G-bendamustine induction was 60% and the CR rate in patients who received G-CHOP induction was 70%. Most patients were progression-free at 32 months of median follow-up. There were some cases of clinically relevant neutropenia (about 14% of patients who received G-bendamustine).[7] These data have led to a phase 3 study (GALLIUM) being conducted now to further evaluate the difference between rituximab and obinutuzumab when we combine them with chemotherapeutic agents in untreated indolent lymphoma.

Preliminary results of a phase 2 trial in FL of ibrutinib, an oral agent that inhibits Bruton's tyrosine kinase (BTK), were presented at this year's meeting. Forty patients with relapsed/refractory FL received continuous dosing of ibrutinib 560 mg/day in 28-day cycles until progression or intolerability. The ORR was 28%, which included a 5% CR rate, revealing modest activity. The levels of activity seen with ibrutinib have been higher in relapsed/refractory chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (for which the drug is already approved by the FDA). An interesting part of the current study, however, is that the response rate was higher (42%) in rituximab-sensitive patients, but the response rate was only 6% in patients who were rituximab-refractory. It appears that these patients with rituximab-refractory disease are more resistant to ibrutinib activity for some reason.[8] Further research will be needed to clarify these results, along with research into combination therapies to determine the optimal utilization of ibrutinib-based therapy for FL.

A phase 1 evaluation of duvelisib (IPI-145), which is an oral PI3 kinase-γ and -δ inhibitor, was conducted in patients with relapsed/refractory indolent lymphoma. Of the 36 patients treated with duvelisib, which was safely dosed at 25 mg twice a day, most had FL. The safety profile was found to be acceptable, with most patients having only grade 1 or 2 toxicity. As is common with the PI3K-δ inhibitor idelalisib, transient increases were seen in the liver enzymes ALT and AST with duvelisib. Neutropenia or pneumonia was seen in about 11%, which were grade 3 or 4 in some patients.[9] A total of 13 of 18 (72%) patients had objective responses. Of these 18, 6 (33%) achieved CR. The median PFS was not reached, but the observation time is still relatively short and so it will have to be monitored further.[9] Additional phase 2 and phase 3 studies evaluating this dose (25 mg twice daily) in patients with indolent lymphoma as monotherapy or in combination with rituximab are currently ongoing.

Mature follow-up data from a phase 2 trial of idelalisib in heavily pretreated patients (median of 4 prior therapies) with double-refractory (to both rituximab and an alkylating agent) indolent lymphoma were presented. A total of 126 patients received oral idelalisib 150 mg twice daily continuously until progression or intolerability. There was a 58% ORR out of 125 patients, with a 56% response in patients with FL and 61% in small lymphocytic lymphoma (SLL); responses were also seen in some of the small numbers of patients with marginal zone lymphoma (MZL) or lymphoplasmacytic lymphoma. The median DOR was found to be 12.5 months. The safety profile was similar to previous reports of idelalisib safety. Phase 3 trials of idelalisib in combination with rituximab or bendamustine plus rituximab are ongoing.[10]

In a small phase 1b study, 20 patients with relapsed or refractory grade 1, 2, or 3a FL were treated with a total of 8 fixed doses of obinutuzumab (GA-101) 1000 mg in combination with lenalidomide in cohorts from 10 to 25 mg for 6 cycles. The maximum tolerated dose (MTD) was not reached. The recommended lenalidomide dose was chosen to be 20 mg because there was more significant neutropenia between cycles 2 and 6 with 25 mg dosing. The combination was well tolerated overall. In the 19 evaluable patients, there was a 63% ORR, which interestingly included about 58% CRs.[11] Currently, studies are assessing the efficacy of the 20-mg dose of lenalidomide plus the obinutuzumab schedule in patients with relapsed/refractory FL and in patients with relapsed/refractory aggressive lymphomas (including those with either DLBCL or MCL).

Mantle Cell Lymphoma

Mature findings were revealed for a phase 2 study that was presented about a year ago of the biological doublet of lenalidomide plus rituximab as initial treatment for MCL. Patients received induction therapy, and those who responded would also continue on the combination until progression of disease. These patients represented typical cases of MCL that were in need of initial therapy. No new toxicity was seen in the 38 treated patients, but patients did experience cytopenias, as is expected with lenalidomide therapy. Patients had evidence of grade 1 or 2 infections that responded to antibiotic therapy. Efficacy results in the intent-to-treat (ITT) population were quite impressive: 84% ORR,

TABLE. Selected Lymphoma Abstracts: ASH 2014

Author/Abstract Number	Comparison	Results Overview
Diffuse Large B-Cell Lymphoma		
Czuczman/628[2]	• R/R disease • Single-agent lenalidomide vs IC • GCB subgroup (n = 50) • Non-GCB/ABC subgroup (n = 50)	• Results suggest some enrichment of clinical benefit (PFS, OS) with single-agent lenalidomide in the non-GCB population; difference appears more pronounced in the ABC population • Data did not meet prespecified criterion to advance to phase 3 trial
Bartlett/629[4]	• Phase 2; pts with undetectable CD30; N = 51 • Brentuximab vedotin every 3 weeks	• ORR 31%, including 10% CR • Median DOR 1.9 months • Median PFS 1.4 months
Van Imhoff/630[5]	• Phase 3; R/R disease, autologous stem cell transplant-eligible pts • Ofatumumab-DHAP: n = 222 • Rituximab-DHAP: n = 225	• No difference in efficacy between the 2 treatment arms
Follicular Lymphoma		
Kimby/799[6]	• R/R or newly diagnosed, untreated disease; N = 154 • Single-agent rituximab vs rituximab plus lenalidomide 15 mg/day for 19 weeks	• ORR: 19% rituximab-lenalidomide vs 61% rituximab only • CR: 36% rituximab-lenalidomide vs 25% rituximab only
Dyer/1743[7]	• Phase 1b maintenance phase; first-line, follicular non-Hodgkin lymphoma • Obinutuzumab-CHOP: n = 41 • Obinutuzumab-bendamustine: n = 40 • Responding pts received obinutuzumab 1000 mg maintenance every 3 months for 2 years or until progression (n = 36 per arm)	At the end of maintenance therapy: • CR: 60% obinutuzumab-bendamustine vs 70% obinutuzumab-CHOP • Clinically-relevant neutropenia: approximately 14% in obinutuzumab-bendamustine group
Bartlett/800[8]	• Phase 2, preliminary results; R/R disease • Ibrutinib 560 mg/day in 28 day cycles • N = 40	• ORR, 28%, including 5% CR • Response rate: 42% in rituximab-sensitive pts vs 6% in rituximab-refractory pts
Flinn/802[9]	• Phase 1, R/R indolent lymphoma • Duvelisib, safely dosed at 25 mg twice daily; n = 36	• ORR: 72%, including 33% CR • Median PFS: not reached • Transient increases in ALT and AST • Neutropenia or pneumonia: 11% (some grade 3 or 4)
Gopal/1708[10]	• Phase 2 double-refractory indolent lymphoma • Idelalisib 150 mg twice daily	• ORR: 58%: 56% in FL; 61% in SLL • Median DOR: 12.5 months
Morschhauser/4458[11]	• Phase 1 b, R/R FL grade 1, 2, or 3a • N = 19 evaluable pts • Obinutuzumab,1000 mg; 8 fixed doses plus lenalidomide • Cohorts from 10 mg to 25 mg for 6 cycles	• MTD: not reached • ORR; 63%, including 58% CR • Recommended lenalidomide dose chosen: 20 mg
Mantle Cell Lymphoma		
Ruan/625[12]	• Phase 2 • Lenalidomide plus rituximab as initial treatment	ITT population: • ORR: 84%, with 55% CR • Median time to PR: 3 months • Median time to CR: 11 months • 2-year PFS: 85%
Trneny/626[13]	• Phase 2; R/R disease • N = 254 • Lenalidomide vs IC • Crossover to lenalidomide allowed on progression	• ORR: 40 % lenalidomide vs 11% IC • Median PFS: 9 months lenalidomide vs 5 months IC • Median DOR: 16 months lenalidomide vs 10 months IC • OS: 28 months lenalidomide vs 21 months IC
Wang/627[14]	• Phase 2; relapsed disease • Ibrutinib and rituximab; after 2 years, ibrutinib alone	• ORR: 68%, 40% CR • Proliferation or Ki-67 index <50% in MCL cells: ORR 100% • Ki-67 index ≥50%: ORR 50%

TABLE. Selected Lymphoma Abstracts: ASH 2014 (continued)

Author/Abstract Number	Comparison	Results Overview
T-Cell Lymphoma		
Dupuis/504[15]	• Phase 1/2 trial; previously untreated PTCL; n = 18 in phase 1b; n =19 in phase 2 • Romidepsin plus CHOP	• ORR: 68%, including 51% CR • Estimated 12-month PFS: 57% • Estimated 12-month OS: 82% • Significant hematologic toxicities, including grade 3 and 4 events: grade 3/4 neutropenia and thrombocytopenia
Chronic Lymphocytic Leukemia		
Zelenetz/1986[16]	• Phase 2, previously untreated pts age ≥65 years with either CLL or SLL • Idelalisib monotherapy	• ORR: 87%, consisting of 47% PR and 40% PR + lymphocytosis rate
O'Brien/327[17]	• Phase 2, open label, RESONATE™-17 trial; pts with R/R CLL/SLL with 17p deletion • Ibrutinib 420 mg orally once daily	• ORR: 83% • 12-month PFS (median not yet reached): 80%
Sharman/330[19]	• Phase 3; relapsed CLL with 17p deletions and other adverse prognostic factors • Idelalisib plus rituximab vs placebo plus rituximab	• PFS strongly favored idelalisib plus rituximab in all risk subgroups, including genetic risk factors (eg, 17p deletion), as well as disease-related risk factors (eg, Rai stage)
Kovacs/23[20]	• Combined analysis of two phase 3 trials in CLL • FC vs FCR; and FCR vs bendamustine + rituximab (545 pts with MRD)	• MRD plus clinical response predicted PFS more accurately than clinical response alone
Novel Therapies		
Lunning/801[21]	• Heavily pre-treated CLL and B-cell lymphoma • Ublituximab plus TGR-1202	• CLL: ORR, approximately 67% • DLBCL: ORR, 43% (3 of 7 pts), 2 pts with CR
Armand/289[22]	• R/R Hodgkin lymphoma • Nivolumab • N = 23	• ORR: 87% (20 of 23 pts), including 17% CR • 6-month PFS: 86% • Decrease in platelet counts: 20% • Diarrhea, nausea, fatigue or fever: >10%
Lesokhin/291[23]	• Phase 1 preliminary results • Various R/R disease, including FL or DLBCL, and T-cell lymphomas • Nivolumab	• DLBCL: 36% (4 of 11 pts) achieved a response • FL: 40% (4 of 10 pts) achieved a response • Mycosis fungoides: 15% achieved a response (2 of 5 pts) • Multiple myeloma: 0% response (0 of 27 pts)
Moskowitz/290[24]	• Phase 1b • Classical Hodgkin lymphoma after brentuximab vedotin failure • Pembrolizumab every 2 weeks for 6 cycles • N = 15	• ORR: 53% • CR: 20% • PR: 33%

ABC indicates activated B cell; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; CR, complete response; DHAP, cisplatin, cytarabine, dexamethasone; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; GCB, germinal-center B cell; IC, investigator's choice; ITT, intent to treat; MCL, mantle cell lymphoma; MRD, minimal residual disease; MTD, maximum tolerated dose; OS, overall survival; ORR, overall response rate; PR, partial response; pts, patients; PFS, progression-free survival; R/R, relapsed refractory; SLL, small lymphocytic lymphoma.

with 55% of patients achieving CR. Of the 36 evaluable patients, the ORR was 89%, with a 58% CR rate. Notably, the 2-year PFS was 85%.[12] This was the first study to show activity and the feasibility of the combination of lenalidomide and rituximab as frontline therapy for MCL. Patients with higher MCL International Prognostic Index (MIPI) scores or proliferation (or Ki-67) indices typically have lower response rates with other therapies. Interestingly, in this study, patients with poor prognostic scores had similar response rates to those of patients with better prognostic features. These data justify further evaluation of this combination, either by itself or maybe with the integration of other novel agents active in the treatment of patients with MCL.[12]

A phase 2, randomized, multicenter study (MCL-002) of lenalidomide versus best investigator's choice in relapsed/refractory MCL was conducted in 254 patients. Patients received either single-agent lenalidomide 25 mg/day on days 1 through 21 every 28 days until progression or toxicity, or investigator's choice (eg, cytarabine, rituximab, gemcitabine, fludarabine, or chlorambucil). Patients who progressed on one of these agents were allowed to cross over to receive lenalidomide. The ORR with lenalidomide was 40% compared with only 11% with investigator's choice, and median PFS was 9 months to approximately 5 months, re-

spectively. The median DOR was improved with lenalidomide: 16 months versus 10 months (with investigator's choice). There was some improvement in overall survival (OS), with 28 versus 21 months, keeping in mind some patients did cross over, which could confound these results. Since single-agent lenalidomide has already been FDA-approved for the treatment of patients with relapsed/refractory MCL, this is additional data demonstrating definite antitumor activity in this patient population, marking its superiority over standard single-agent chemotherapy alone.[13]

Preliminary results from a phase 2 trial of the combination of ibrutinib and rituximab in patients with relapsed MCL were presented. Patients received ibrutinib 560 mg/day until progression or intolerability combined with rituximab 375 mg/m^2 weekly × 4 (cycle 1) and then 1 dose per cycle (cycles 3 through 8), and then 1 dose every other cycle for up to 2 years. After 2 years, ibrutinib was given as a single agent until progressive disease or intolerance. Definite efficacy of the combination was shown, with a 68% ORR and 40% of patients achieving CR. It was interesting that patients with a proliferation (or Ki-67) index <50% in MCL cells benefited the most, with 34/34 (100%) patients responding. In patients with ≥50% Ki-67, ORR was only 50%. There were also more CRs in patients with lower Ki-67 scores. Therefore, Ki-67 could become a potential biological marker that could help inform us which patients may benefit most from this treatment combination.[14]

T-Cell Lymphoma

One of the more interesting lymphoma studies presented at ASH was of a histone deacetylase (HDAC) inhibitor called romidepsin in combination with CHOP in patients with previously untreated peripheral T-cell lymphoma (PTCL). These are the final results of the phase 1/2 trial. A total of 18 patients were included in the phase 1b trial, with 19 in phase 2. Different dosing cohorts of romidepsin were evaluated with standard CHOP. There was an ORR of 68% (24/35 evaluable patients), including a 51% CR rate. The estimated 12-month PFS was about 57%, and the estimated 12-month OS rate was 82%. Although this study demonstrated that romidepsin can be combined with CHOP, there were also significant hematologic toxicities reported (including grade 3 and 4 events). The majority of patients experienced grade 3/4 neutropenia, and over one-third of the patients had grade 3/4 thrombocytopenia. A significant amount of growth factor was utilized for these patients. But considering that this population is often treated with standard CHOP therapy, the PFS improvement at least seems promising with this combination.[15] A phase 3 study is now comparing CHOP alone versus the combination of romidepsin-CHOP.

Chronic Lymphocytic Leukemia

One abstract from ASH reported a phase 2 trial of idelalisib monotherapy, a PI3K-δ inhibitor, in previously untreated patients ≥65 years with either CLL or SLL. Idelalisib has been approved for use in the relapsed setting, but this study is interesting because it shows definite activity in previously untreated patients. There was an 87% ORR rate in these treatment-naïve older patients, consisting of a 47% partial response (PR) rate and a 40% PR + lymphocytosis rate (ie, patients with evidence of lymphocytes circulating in the blood who still had a ≥50% shrinkage of their adenopathy). As expected of single-agent idelalisib, peripheral lymphocytosis was increased early after initiating therapy. The safety profile was similar to that seen with prior trials, and toxicity was tolerable.[16]

The open-label, phase 2 RESONATE™-17 trial investigated the safety and efficacy of ibrutinib in patients with relapsed/refractory CLL/SLL with 17p deletion. This was the largest prospective trial in this subpopulation, including 144 patients who had received 1 to 4 prior lines of therapy. Oral ibrutinib was given at the typical dosage of 420 mg orally once daily until either unacceptable toxicity or disease progression. The ORR was 83%. The median PFS and DOR were not reached from the short follow-up, but at 12 months, PFS was around 80%.[17] This PFS was similar to the PFS seen in patients treated with fludarabine, cyclophosphamide, and rituximab (FCR) as combination upfront therapy in CLL.[18] It should be noted that ibrutinib is also FDA-approved for patients with 17p deletion in the setting of newly diagnosed, previously untreated CLL.

A second interim analysis of a phase 3 study of idelalisib plus rituximab in relapsed CLL was available, showing efficacy analyses in patients with 17p deletions and other adverse prognostic factors. This trial demonstrated that idelalisib has significant activity in this population. Patients in this trial had similar efficacy with idelalisib plus rituximab in the presence or absence of high-risk genomic abnormalities. Patients with, for example, a 17p deletion, achieved similar results as those with better prognostic factors, without new toxicity.[19]

One of the most important things about CLL to take home from this ASH meeting was that there appears to be potential value in measuring minimal residual disease (MRD) status as a CLL response evaluation. A combined analysis of 2 large phase 3 trials (CLL-8 and CLL-10) of the German CLL Study Group looked at patients who had received fludarabine and cyclophosphamide (FC) versus FCR in one study or FCR treatment versus bendamustine and rituximab in the other. There were almost 1400 patients at the outset, with 545 patients with MRD analysis. MRD and clinical response were both strong predictors, but the best combination was getting MRD in combination with clinical response, which predicted PFS more accurately than just looking at clinical response. In other words, evaluating just CR or PR was not as meaningful as achieving a MRD state was (eg, MRD-negative CRs achieved a larger PFS than MRD-positive CRs).[20]

It was also interesting that splenomegaly as the sole abnormality at the end of the treatment response did not impact PFS in patients who were MRD-negative. In other words, these patients still had splenomegaly and were considered to have a clinical PR, but as long as the blood was completely cleared down to MRD, those patients actually did as well as patients who had achieved a clinical CR. The patients that will fare the best are ones who have both a decrease in the nodal disease and a clearing of the blood of these abnormal CD19+, CD5+, CD23+ cells (the typical phenotype of CLL). We may be seeing more of this

evaluation in the future, possibly included as part of prospective trials, as not just the achievement of a clinical CR, but more so the "quality" of the CR (ie, MRD status) may actually be a very important end point in future CLL clinical trials.[20]

Novel Lymphoma Therapies

A new CD20 antibody, ublituximab, was combined with a novel, next-generation PI3K-δ inhibitor, TGR-1202 in heavily pretreated and high-risk CLL and B-cell lymphoma. Ublituximab, a second-generation monoclonal antibody, binds to a unique CD20 epitope compared with the other CD20 antibodies, such as rituximab or ofatumumab. It is interesting that the PI3K-δ inhibitor, TGR-1202, is administered only once a day (800 mg), whereas patients treated with idelalisib typically receive it twice daily. Also of note is that there was no significant increase in liver enzymes with this combination, which is usually expected with PI3K-δ inhibition using idelalisib. It could be that this is secondary to its unique molecular structure; it will be interesting to see future updates. In CLL, the ORR was about 67%. The patient numbers were small; for example, in DLBCL there was a 43% ORR, but that was in only 3 out of 7 patients. But still, there appears to be a preliminary positive signal of activity, including 2 patients with DLBCL who achieved CR. There has been no liver toxicity to date in 87 patients treated with the PI3K-δ inhibitor.[21]

A tremendous amount of excitement has been generated by the so-called immune checkpoint inhibitors–in particular, inhibitors of the programmed death 1 (PD-1) receptor or programmed death ligand 1 (PD-L1). Many tumors actually have these ligands, and once the ligand binds to the PD-1 receptor on T cells, the activity of the T cell is downregulated. Therefore, if we can block the interaction between the PD-1 receptor and the PD-L1 ligand, the innate immune system will remain intact.

The PD-1 inhibitor nivolumab, which is a human IgG4 monoclonal antibody that blocks PD-1, has been studied in patients with relapsed/refractory Hodgkin lymphoma. Out of 23 patients, 20 responded, so the ORR was 87%, including a 17% CR rate and a 6-month PFS rate of 86%, which are remarkable numbers. There was some toxicity, the most common being rash, some decrease (20%) in platelet counts, and >10% of patients with either diarrhea, nausea, fatigue, or fever. But, in general, the agent was very well tolerated. These results are quite incredible in this heavily pretreated patient population, and it is amazing to have this kind of a single-agent response rate simply by bestowing the ability to allow the immune system to do its job. Based on these important results, the FDA granted nivolumab breakthrough status in relapsed classical Hodgkin lymphoma, and there is a large, multinational phase 2 trial of this therapy currently under way.[22]

In addition to Hodgkin lymphoma, preliminary results of a phase 1 study of nivolumab were also described in various relapsed/refractory lymphoid malignancies, including B-cell lymphomas, either FL or DLBCL, or T-cell lymphomas–such as mycosis fungoides or PTCL–as well as a number of patients with multiple myeloma. Of the evaluable patients, 4 out of 11 (36%) patients with DLBCL achieved a response. Out of the 10 patients with FL, responses were seen in 4 (40%). Roughly 15% of patients with mycosis fungoides and 40% with PTCL responded. It should be noted that 0 out of the 27 patients with multiple myeloma had an objective response to treatment with this novel agent. Additional multicenter, phase 2 trials are ongoing, in particular in DLBCL and FL.[23]

Another anti-PD-1 monoclonal antibody called pembrolizumab was studied in a phase 1b trial in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. Patients (N = 15) received pembrolizumab every 2 weeks for 6 cycles of treatment. Re-staging was demonstrated at week 12 with a 53% ORR, 20% CRs, and 33% PRs. Again, it is very exciting that, by not allowing the PD-L1 ligand to bind to the PD-1 receptor and suppress T cell activity, we can allow the T cells to do the job that they were born to do.[24]

Conclusion

At ASH, we were exposed to updated data for existing treatments and exciting data with investigational combinations utilized to treat various lymphoid neoplasms. In addition, new data were revealed on some of the novel targeted agents, in particular checkpoint inhibitors, which harness the potential of not blocking the body's immune system to fight cancer, a strategy which has demonstrated very exciting preliminary results in hematologic malignancies, as well as recently in solid tumors.

Affiliation: Myron S. Czuczman, MD, is Professor of Oncology, Chief, Lymphoma/Myeloma Service, Department of Medicine, and Head, Lymphoma Translational Research Laboratory, Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY. In addition, Dr Czuczman is associate editor of *The American Journal of Hematology/Oncology*.

Disclosure: Dr Czuczman has served on advisory committees/review panels or as a consultant for Algeta, Boehringer Ingelheim, Celgene, Gilead, Millennium, MorphoSys, Mundipharma, Teva, and TG Therapeutics, and has received honoraria from Mundipharma.

Address correspondence to: Myron S. Czuczman, MD, Roswell Park Cancer Institute, Elm and Carlton St, Buffalo, NY 14263. Email: Myron.Czuczman@RoswellPark.org.

REFERENCES

1. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. *Cancer*. 2011;117(22):5058-5066.

2. Czuczman MS, Davies A, Linton KM, et al. A phase 2/3 multicenter, randomized study comparing the efficacy and safety of lenalidomide versus investigator's choice in relapsed/refractory DLBCL. *Blood*. 2014;124(21): Abstract 628.

3. Bartlett NL, Sharman JP, Oki Y, et al. A phase 2 study of brentuximab vedotin in patients with relapsed or refractory CD30-positive non-Hodgkin lymphomas: interim results in patients with DLBCL and other B-cell lymphomas. *Blood*.

2013;122(21): Abstract 848.
4. Bartlett NL, Smith MR, Advani R, et al. Brentuximab vedotin monotherapy in DLBCL patients with undetectable CD30: preliminary results from a phase 2 study. *Blood*. 2014;124(21): Abstract 629.
5. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-Cell lymphoma: the Orcharrd Study (OMB110928). *Blood*. 2014;124(21): Abstract 630.
6. Kimby E, Martinelli G, Ostenstad B, et al. Rituximab plus lenalidomide improves the complete remission rate in comparison with rituximab monotherapy in untreated follicular lymphoma patients in need of therapy. Primary endpoint analysis of the randomized phase-2 trial SAKK 35/10. *Blood*. 2014;124(21): Abstract 799.
7. Dyer MJ, Grigg AP, González Díaz M, et al. Obinutuzumab (GA101) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine for the first-line treatment of follicular non-Hodgkin lymphoma: final results from the maintenance phase of the phase Ib GAUDI study. *Blood*. 2014;124(21): Abstract 1743.
8. Bartlett NL, LaPlant BR, Qi J, et al. Ibrutinib monotherapy in relapsed/refractory follicular lymphoma (FL): preliminary results of a phase 2 consortium (P2C) trial. *Blood*. 2014;124(21): Abstract 800.
9. Flinn I, Oki Y, Patel M, et al. A phase 1 evaluation of duvelisib (IPI-145), a PI3K-δ,γ inhibitor, in patients with relapsed/refractory iNHL. *Blood*. 2014;124(21): Abstract 802.
10. Gopal AK, Kahl BS, de Vos S, et al. Mature follow up from a phase 2 study of PI3K-delta inhibitor idelalisib in patients with double (rituximab and alkylating agent)-refractory indolent B-cell non-Hodgkin lymphoma (iNHL). *Blood*. 2014;124(21): Abstract 1708.
11. Morschhauser F, Salles G, Le Gouill S, et al. A phase Ib study of obinutuzumab combined with lenalidomide for relapsed/refractory follicular B-cell lymphoma. *Blood*. 2014;124(21): Abstract 4458.
12. Ruan J, Martin P, Shah BD,et al. Sustained remission with the combination biologic doublet of lenalidomide plus rituximab as initial treatment for mantle cell lymphoma: a multi-center phase II study report. *Blood*. 2014;124(21): Abstract 625.
13. Trneny M, Lamy M, Walewski J, et al. Phase II randomized, multicenter study of lenalidomide vs best investigator's choice in relapsed/refractory mantle cell lymphoma: results of the MCL-002 (SPRINT) study. *Blood*. 2014;124(21): Abstract 626.
14. Wang M (L), Hagemeister F, Westin JR, et al. Ibrutinib and rituximab are an efficacious and safe combination in relapsed mantle cell lymphoma: preliminary results from a phase II clinical trial. *Blood*. 2014;124(21): Abstract 627.
15. Dupuis J, Morschhauser F, Ghesquieres H, et al. Final analysis of the RO-CHOP phase Ib/II study: romidepsin in association with CHOP in patients with peripheral T-cell lymphoma (PTCL). *Blood*. 2014;124(21): Abstract 504.
16. Zelenetz AD, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib monotherapy in previously untreated patients ≥65 years with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). *Blood*. 2014;124(21): Abstract 1986.
17. O'Brien S, Jones JA, Coutre S, et al. Efficacy and safety of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic leukemia with 17p deletion: results from the phase II RESONATE™-17 trial. *Blood*. 2014;124(21): Abstract 327.
18. Hallek M, Fischer K, Fingerle-Rowson G, et al; International Group of Investigators; German Chronic Lymphocytic Leukaemia Study Group. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.
19. Sharman JP, Coutre SE, Furman RR, et al. Second interim analysis of a phase 3 study of idelalisib (ZYDELIG®) plus rituximab (R) for relapsed chronic lymphocytic leukemia (CLL): efficacy analysis in patient subpopulations with del(17p) and other adverse prognostic factors. *Blood*. 2014;124(21): Abstract 330.
20. Kovacs G, Boettcher S, Bahlo J, et al. Value of minimal residual disease (MRD) negative status at response evaluation in chronic lymphocytic leukemia (CLL): combined analysis of two phase III studies of the German CLL Study Group (GCLLSG). *Blood*. 2014;124(21): Abstract 23.
21. Lunning MA, Vose JM, Schreeder MT,etal.Ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody (mAb), in combination with TGR-1202, a next generation once daily PI3kδ inhibitor, demonstrates activity in heavily pre-treated and high-risk chronic lymphocytic leukemia (CLL) and B-cell lymphoma. *Blood*. 2014;124(21): Abstract 801.
22. Armand P, Ansell SM, Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory Hodgkin lymphoma - preliminary safety, efficacy and biomarker results of a phase I study. *Blood*. 2014;124(21): Abstract 289.
23. Lesokhin AM, Ansell SM, Armand P, et al. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. *Blood*. 2014;124(21): Abstract 291.
24. Moskowitz CH, Ribrag V, Michot J-M, et al. PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013). *Blood*. 2014;124(21): Abstract 290.