Highlights in Leukemia and Lymphoma

Commentary by Susan O'Brien, MD

Nivolumab Outperforms Brentuximab Vedotin in Newly Diagnosed Advanced Hodgkin Lymphoma

Nivolumab (Opdivo, Bristol Myers Squibb) plus doxorubicin, vinblastine, and dacarbazine (AVD) significantly improved progression-free survival (PFS) and was better tolerated compared with brentuximab vedotin (Adcetris, Seagen)/AVD in patients with newly diagnosed advanced Hodgkin lymphoma (HL), according to the second interim analysis of the SWOG S1826 trial.

The phase 3 trial, which was presented by Dr Alex F. Herrera, enrolled adult and pediatric (age ≥12 years) patients with untreated stage 3 to 4 classic HL from July 2019 to October 2022. A total of 976 patients were randomized in a 1:1 ratio to receive 6 cycles of either nivolumab/AVD (n=489) or brentuximab vedotin/AVD (n=487). Granulocyte colony–stimulator factor (G-CSF) for neutropenia prophylaxis was required in the brentuximab vedotin arm and optional in the nivolumab arm. The primary endpoint was PFS.

In the second interim analysis, at a median follow-up of 12.1 months, the 1-year PFS was longer in the nivolumab arm than in the brentuximab vedotin arm, at 94% vs 86%, respectively (hazard ratio [HR], 0.48; 99% CI, 0.27-0.87; *P*=.0005). This PFS benefit was consistent across subgroups. Event-free survival (EFS) also was higher in the nivolumab arm than in the brentuximab vedotin arm. There was a trend toward longer overall survival (OS) with nivolumab vs brentuximab vedotin, but it was not statistically significant.

Treatment with nivolumab/AVD was well-tolerated, with few immune-related adverse events (AEs). There were 4 deaths (3 due to AEs) in the nivolumab group vs 11 deaths (7 due to AEs) in the brentuximab vedotin group. Patients in the nivolumab group were more likely than those in the brentuximab vedotin group to experience neutropenia (55% vs 32%) but less likely to receive G-CSF (54% vs 95%) or experience bone pain (8% vs 20%). Less than 1% of patients received end-of-treatment radiation therapy (RT).

Dr Herrera concluded that S1826 represents "a key step toward harmonizing pediatric and adult therapy of Hodgkin lymphoma." He added that based on these data, "nivolumab/AVD is poised to be a new standard" for the treatment of advanced HL.

Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab (N)-AVD versus brentuximab vedotin (BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL) [ASCO abstract LBA4). *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: It is not surprising that this abstract was presented at the ASCO Plenary Session, because the results are practice changing. The current standard of care for advanced HL is brentuximab vedotin/AVD, which has recently replaced ABVD as the most effective frontline regimen. In this trial, substituting a checkpoint inhibitor, nivolumab, for brentuximab vedotin resulted in significantly better PFS. Nivolumab/AVD also caused significantly less peripheral neuropathy, which can be a debilitating side effect for many patients. Finally, it is the first trial ever conducted encompassing the entire US Intergroup plus the Children's Oncology Group, so the standard of care (SOC) can be changed for both pediatric patients and adults at the same time.

Study Supports Omission of Radiation Therapy in Some Patients With Primary Mediastinal B-Cell Lymphoma

Patients with primary mediastinal B-cell lymphoma (PMBCL) who experience a complete metabolic response (CMR) after immunochemotherapy may be able to safely omit RT, according to results from the IELSG37 trial. This is the largest prospective study of PMBCL ever conducted, said presenter Dr Emanuele Zucca, although the event rate did not reach the assumed level.

The study enrolled 545 patients with newly diagnosed PMBCL from 74 centers in 13 countries. After receiving standard immunochemotherapy with rituximab and doxorubicin, the 268 patients who experienced a CMR based on a central review of positron emission (PET)/computed tomography (CT) scans were randomly assigned to observation (n=132) or mediastinal RT at 30 Gy (n=136). Randomization was stratified by sex, chemotherapy regimen, country, and PET/CT score. The primary endpoint was PFS after randomization.

Although the observed number of events was considerably lower than expected after a median follow-up of 30 months, the Independent Data Monitoring Committee recommended completing the planned total accrual without increasing the study size or duration. The researchers found that the difference in PFS at 30 months (98.5% in the RT arm and 96.2% in the observation arm) was

not statistically significant and was clinically not relevant. Similarly, the 5-year OS was 99% in both arms. Even if the observed difference were describing the true (real) benefit of RT, more than 126 patients would need to be treated to avoid a single relapse. Longer follow-up is needed to examine late toxicity, as RT is known to increase the risk of second malignancies, coronary heart disease, and valvular heart disease.

Dr Zucca concluded that mediastinal RT "may be safely omitted in patients with complete metabolic response after frontline immunochemotherapy containing rituximab and doxorubicin."

Zucca E, Davies A, Kryachok I, et al. Observation vs. radiotherapy in primary mediastinal B-cell lymphoma patients with complete response to standard immunochemotherapy: the IELSG37 randomized trial [ASCO abstract LBA7505]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: PMBCL is an uncommon subset of diffuse LBCL (DLBCL) characterized by the involvement of large mediastinal masses. In cases of aggressive lymphoma, the question often arises of whether bulky lymph node sites should be radiated to consolidate remissions achieved with chemoimmunotherapy. Whether this is done or not varies from center to center. This trial is important because it was the largest randomized trial ever conducted in patients with PMBCL. It led to the satisfying conclusion that mediastinal radiation is not needed after chemoimmunotherapy. That is important because there are often significant late side effects resulting from radiation, including second malignancies and cardiac disorders. Notably, at a median follow-up of 5 years, the 3 severe cardiac events and 3 second cancers were all in patients randomized to radiation. PFS was superb with either approach and survival was 99% at 30 months. Given the favorable survival, minimizing late toxicity by avoiding radiation could have a further significant impact on OS over time.

Second-Line Axicabtagene Ciloleucel Improves OS in Early Relapsed or Refractory Large B-Cell Lymphoma

Axicabtagene ciloleucel, also known as axi-cel (Yescarta, Kite), significantly improves OS compared with SOC treatment as second-line therapy in patients with early relapsed or refractory large B-cell lymphoma (R/R LBCL), according to the primary OS analysis of the phase 3 ZUMA-7 trial. The previous analysis of ZUMA-7 showed that axi-cel, a chimeric antigen receptor (CAR) T-cell therapy, improved the primary endpoint of EFS in these patients.

For the study, Dr Jason Westin and colleagues enrolled 359 patients (median age, 58 years) at 77 sites who had LBCL that was R/R after 1 year or less of first-line therapy. All patients intended to undergo high-dose chemotherapy (HDT) plus autologous stem cell transplant (ASCT). Patients were randomly assigned in a 1:1 ratio to conditioning chemotherapy plus axi-cel (n=180) or SOC treatment with platinum-based chemoimmunotherapy (n=179). In the SOC group, patients who responded to treatment proceeded to HDT-ASCT and nonresponders received additional treatment. A total of 94% of patients in the axi-cel group received axi-cel and 36% of those in the SOC group received HDT-ASCT.

In the previous analysis, at a median follow-up of 24.9 months, median EFS was higher in the axi-cel group than in the SOC group, at 8.3 vs 2.0, respectively (HR, 0.398; 95% CI, 0.308-0.514; $P<.001$). In the current analysis, with a median follow-up of 47.2 months, median OS was significantly higher in the axi-cel group than the SOC group, at not reached vs 31.1 months, respectively (HR, 0.726; 95% CI, 0.540-0.977; one-sided $P=.017$). The survival benefit favoring axi-cel was similar across prespecified subgroups. Median PFS by investigator also favored axi-cel over SOC, at 14.7 vs 3.7 months, respectively (HR, 0.506; 95% CI, 0.383-0.669; $P=.001$). AEs were consistent with those from the primary EFS analysis.

Dr Westin said that ZUMA-7 confirms that axi-cel is a second-line SOC for patients with R/R LBCL. He added that "ZUMA-7 is the first randomized trial in any cancer to show an overall survival benefit for a CAR T-cell therapy over an existing standard of care." The results were simultaneously published in the *New England Journal of Medicine*.

Westin J, Oluwole OO, Kersten MJ, et al. Primary overall survival analysis of the phase 3 randomized ZUMA-7 study of axicabtagene ciloleucel versus standard-of-care therapy in relapsed/refractory large B-cell lymphoma [ASCO abstract LBA107]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The ZUMA-7 trial led to US Food and Drug Administration/European Medicines Agency approval of this therapy for patients with DLBCL relapsing within 12 months of frontline therapy or after 2 prior lines of therapy. Approval was based on improved EFS with axi-cel, as published in the *New England Journal of Medicine* in 2022. The current analysis looked at OS, and the findings were interesting. The OS with axi-cel was better compared with SOC chemoimmunotherapy and ASCT, a surprisingly positive outcome. Historically, the OS in primary refractory DLBCL, which included 70% of the patients in ZUMA-7, was less than 1 year. Here, the median OS in the SOC arm was 31 months vs not reached in the axi-cel arm. Thus, survival in the SOC arm was much better than expected based on historical data. Around 57% of the SOC patients later received cellular immunotherapy off protocol, which appears to have improved the OS significantly in that group. At 4 years,

the OS of 54.6% in the axi-cel group and 46% in the SOC group, strongly suggesting that axi-cel CAR T-cell therapy is a curative option for relapsed DLBCL. Notably, this was the first trial in nearly 30 years in the second-line DLBCL setting to show improved OS.

Lisocabtagene Maraleucel Demonstrates Durable Responses in R/R CLL/SLL After BTK Inhibition

Lisocabtagene maraleucel, also known as liso-cel (Breyanzi, Bristol Myers Squibb), demonstrated rapid, deep, and durable responses and a manageable safety profile in patients with heavily pretreated, high-risk R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to results from the phase 1/2 TRANSCEND CLL 004 trial.

The trial, which was presented by Dr Tanya Siddiqi, enrolled 137 patients with R/R CLL/SLL who had received at least 2 prior lines of therapy for high-risk disease and at least 3 prior lines of therapy for standard-risk disease. All patients had disease that had progressed on a Bruton tyrosine kinase (BTK) inhibitor or were ineligible for BTK inhibition, and had a European Cooperative Oncology Group performance status of 0 to 1. Patients received liso-cel at either 50 (dose level 1) or 100 (dose level 2) × 10^6 CAR T cells. The primary endpoint was rate of complete response (CR) and CR with incomplete marrow recovery (CRi) by an Independent Review Committee (IRC).

At a median follow-up of 21.1 months, the IRC-assessed CR/CRi rate among the 87 patients in the full study population who received liso-cel at dose level 2 was 18.4% (95% CI, 10.9-28.1). The overall response rate (ORR) was 47.1% and the rate of undetectable measurable residual disease (MRD) was 64.4% in blood and 58.6% in marrow. The median duration of response (DOR) was 35.3 months and the median PFS was 18.0 months. Among a group of 49 patients who received liso-cel at dose level 2 and had experienced disease progression despite treatment with both BTK inhibition and venetoclax, the IRC-assessed CR/CRi rate was 18.4% (95% CI, 8.8-32.0), the ORR was 42.9% (95% CI, 28.8-57.8), the rate of undetectable MRD was 63.3% in blood and 59.2% in marrow, the median DOR was 35.3 months, and the median PFS was 11.9 months.

Among the 117 patients who received liso-cel, the most common grade 3 or higher treatment-emergent AEs were neutropenia (61%), anemia (52%), and thrombocytopenia (41%). The rate of grade 3 or higher cytokine release syndrome was 9% and the rate of grade 3 or nigher neurologic events was 18%. There was 1 death related to liso-cel.

"Overall, I think these results support the use of liso-cel as a potential new treatment option in relapsed/refractory CLL patients, especially after prior BTK inhibitor therapy," concluded Dr Siddiqi.

Siddiqi T, Maloney DG, Kenderian S, et al. Lisocabtagene maraleucel (liso-cel) in R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): primary analysis of TRANSCEND CLL 004 [ASCO abstract 7501]. *J Clin Oncol.* 2023;41(16)(suppl).

Commentary: The TRANSCEND trial results are encouraging, particularly for CLL patients who have progressed on a BTK inhibitor and venetoclax. Many of these patients have also progressed on chemoimmunotherapy, but with little use of chemoimmunotherapy in the frontline setting and an increased use of small molecules as initial therapy, this group will continue to proliferate. Currently, treatment options are very limited, and no SOC therapy is available, leading to short survival. The ORR of 43% with a CR rate of 18% achieved with liso-cel is quite impressive for this highly refractory population, some of whom had undergone 5 prior regimens. Notably, the remissions achieved with liso-cel seem to be durable, making it an effective stand-alone therapy as well as a potential bridge to stem cell transplant. The patients who achieved a CR had an impressive durability of response, with no relapses at a median follow-up of 1 1/2 years. The typical CAR T-cell effects of cytokine release syndrome and neurotoxicity were seen but were rarely severe. Of note, the oldest patient in this trial was 88, so even in the CLL population where most patients are older, CAR T-cell therapy with liso-cel appears to be a potential new treatment option.

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