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A SPECIAL MEETING REVIEW EDITION

Highlights in Hodgkin Lymphoma From the 63rd American Society of Hematology Annual Meeting and Exposition

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Special Reporting on:

- Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for Advanced-Stage Classical Hodgkin Lymphoma: Preliminary Safety Results From the Single-Arm Phase 2 Study (SGN35-027 Part B)
- Frontline Treatment With Single-Agent Pembrolizumab Followed by AVD Chemotherapy for Classical Hodgkin Lymphoma: Updated Results and Correlative Analysis
- Novel Salvage Regimens Lead to Better Response and Survival in Relapsed/Refractory Classic Hodgkin Lymphoma After Autologous Stem Cell Transplant
- Effect of Brentuximab Vedotin Addition to Chemotherapy and Prognostic Factors in Patients With Relapsed/Refractory Hodgkin Lymphoma: A Large Multi-Trial Analysis Based on Individual Patient Data
- Pembrolizumab Added to ICE Chemotherapy Results in High Complete Metabolic Response Rates in Relapsed/Refractory Classic Hodgkin Lymphoma: A Multi-Institutional Phase 2 Trial
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PLUS Meeting Abstract Summaries

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Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine for Advanced-Stage Classical Hodgkin Lymphoma: Preliminary Safety Results From the Single-Arm Phase 2 Study (SGN35-027 Part B)

Brentuximab vedotin is an antibody–drug conjugate that is directed at CD30 molecules expressed by the Reed-Sternberg cell. This treatment induces immunogenic cell death.[1] Nivolumab inhibits the expression of programmed death 1 (PD-1) and antitumor activity, thereby enhancing T-cell activity, T-cell proliferation, and cytokine production. Prior studies have demonstrated promising results with brentuximab vedotin in combination with nivolumab as first salvage therapy and as first-line treatment in older adults with Hodgkin lymphoma.[2,3] Treatment with brentuximab vedotin plus doxorubicin and dacarbazine has led to robust rates of complete remission (97%) and estimates of progression-free survival (PFS; 91%) in patients with early-stage classical Hodgkin lymphoma.[4]

Lee and colleagues presented the safety and efficacy analysis from part B of the SGN35-027 study.[1] This multicenter phase 2 trial investigated first-line treatment with up to 6 cycles of brentuximab vedotin (1.2 mg/kg) and nivolumab (240 mg), plus doxorubicin (25 mg/m^2) and dacarbazine (375 mg/m^2), in 58 patients with advanced-stage classical Hodgkin lymphoma.[1] The study drugs were administered via intravenous infusion on days 1 and 15 of each 28-day cycle. The primary endpoint was the rate of complete metabolic response (CMR) at the end of therapy.

The patients' median age was 35 years. The disease was stage 3 in 18% of patients and stage 4 in 57% of patients. All patients but one received at least 1 dose of study treatment.[1] The patients received a median of 12 doses each of brentuximab vedotin and nivolumab (range, 1-12 doses).

Response assessments were performed with positron emission tomography (PET) and diagnostic-quality computed tomography (CT) scans on days 25 to 28 of cycle 2 (interim assessment) and at the end of therapy.[1] The interim assessment revealed an overall response rate (ORR) of 96% and a complete response (CR) rate of 74%. At the end of therapy, the ORR was 93% and the CR rate was 88%. This analysis excluded a participant with CMR at the end of therapy, since the event occurred after data cutoff. More than 90% of patients experienced a reduction in tumor size of 50% or higher (measured by the sum of the product of the greatest diameter; Figure 1).

Most patients experienced treatment-related adverse events (AEs). The most common of these events consisted of nausea (65%), fatigue (46%), and

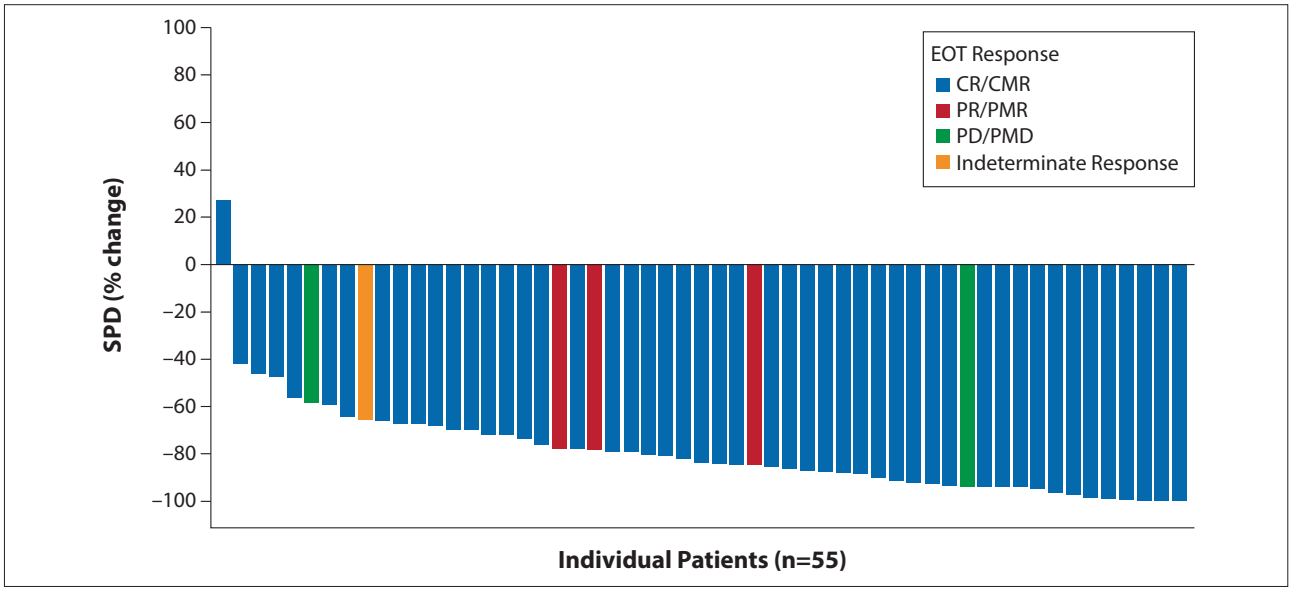

Figure 1. Reduction in tumor size among patients with advanced-stage classical Hodgkin lymphoma treated with brentuximab vedotin and nivolumab plus doxorubicin and dacarbazine in the phase 2 SGN35-027 study. CMR, complete metabolic response; CR, complete response; EOT, end of treatment; PD, progressive disease; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response. Lee HJ et al. ASH abstract 2454. *Blood*. 2021;138(suppl 1).[1]

peripheral sensory neuropathy (39%). Peripheral neuropathy was primarily low grade; only 4% of events were grade 3 or higher. No patients discontinued treatment owing to peripheral neuropathy. There were no cases of febrile neutropenia. No patients died during the study.

Among the 18 patients (32%) who developed immune-mediated AEs, 8 required treatment with corticosteroids.[1] Two patients (4%) developed treatment-emergent immune-mediated pneumonitis, which resolved fully in both cases. Hypothyroidism occurred in 7% of patients, and colitis occurred in 4% of patients. Eight patients (14%) experienced treatment-related serious AEs of pneumonitis (5%) and pyrexia (4%). One patient with hypophysitis and aseptic meningitis discontinued treatment after cycle 1. Another patient developed autoimmune hepatitis, which led to the discontinuation of nivolumab.

The investigators concluded that brentuximab vedotin and nivolumab used in combination with doxorubicin and dacarbazine is a promising regimen for the first-line treatment of high-risk patients with advanced-stage classical Hodgkin lymphoma.[1] The low rate of grade 3 peripheral neuropathy and the lack of febrile neutropenia compare favorably with other first-line regimens. Enrollment of treatment-naive patients with early-stage classical Hodgkin lymphoma (stage 1 or 2) without bulky mediastinal disease is ongoing in part C of the SGN35-027 study.[5]

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Frontline Treatment With Single-Agent Pembrolizumab Followed by AVD Chemotherapy for Classical Hodgkin Lymphoma: Updated Results and Correlative Analysis

Classical Hodgkin lymphoma is characterized by genomic copy number alterations of chromosome 9p24.1, which leads to increased expression of programmed death ligands 1 (PD-L1) and 2 (PD-L2).[1] Blocking PD-1 with pembrolizumab leads to excellent responses. However, biomarkers predicting depth of response are limited.

Allen and colleagues presented updated results and a correlative analysis of the sequential use of pembrolizumab and doxorubicin, vinblastine, and dacarbazine (AVD) in newly diagnosed patients with early unfavorable or advanced-stage classical Hodgkin lymphoma.[2,3] The primary endpoint was the CMR rate according to PET/CR after 3 doses of pembrolizumab monotherapy. Thirty patients received 3 doses of pembrolizumab monotherapy and then underwent PET/CT to assess for CMR. The patients then received 4 to 6 cycles of AVD, with PET/CT assessments after the second and final cycles. Patients will continue to be monitored every 3 months for 2 years after the end of treatment, with CT performed every 6 months. Correlative analyses were performed

ABSTRACT SUMMARY Brentuximab Vedotin in Combination With Nivolumab, Doxorubicin, and Dacarbazine in Newly Diagnosed Patients With Advanced-Stage Hodgkin Lymphoma (SGN35-027, Trial in Progress)

Flinn and colleagues hypothesized that the combination of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine might result in high response rates with potentially less toxicity than regimens containing vinblastine (Abstract 1369). SGN35-027 is an open-label, multipart, multicenter phase 2 trial of brentuximab vedotin in treatment-naive patients with early-stage classical Hodgkin lymphoma. Parts A and B have completed enrollment. Enrollment in part C is ongoing at 54 study sites in the United States, Australia, and Spain. Approximately 150 patients will receive brentuximab vedotin (1.2 mg/kg), nivolumab (240 mg), doxorubicin (25 mg/m^2), and dacarbazine (375 mg/m^2) in part C. Each treatment will be administered separately by intravenous infusion on days 1 and 15 of each 28-day cycle, for up to 4 cycles. The primary endpoint, the CR rate at the end of treatment, will be assessed by CT. Additional efficacy endpoints and safety assessments will evaluate whether treatment with brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine improves response rates and tolerability compared with vinblastine-containing regimens.

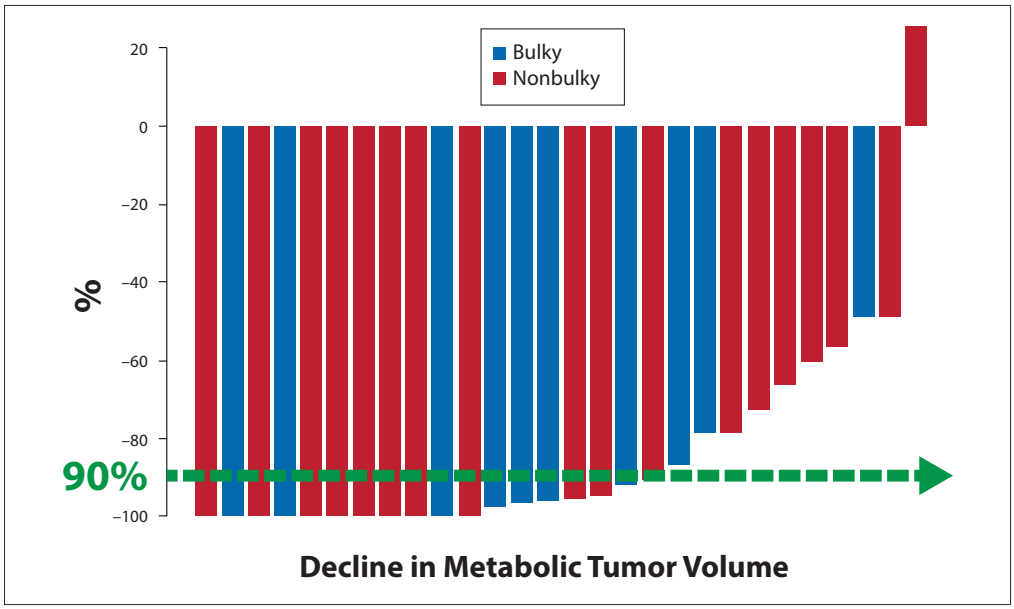

Figure 2. Decline in metabolic tumor volume among newly diagnosed patients with early unfavorable or advanced-stage classical Hodgkin lymphoma who received frontline treatment with sequential pembrolizumab and doxorubicin, vinblastine, and dacarbazine in a correlative analysis. Adapted from Allen PB et al. ASH abstract 231. *Blood*. 2021;138(suppl 1).[3]

by immunohistochemistry for PD-1 pathway markers and by fluorescence in situ hybridization (FISH) to detect chromosome 9p24.1 alterations.

The patients' median age was 29 years, and 13% were older than 60 years. Advanced-stage disease was reported in 60%.[2] Approximately half of patients had B symptoms at diagnosis, elevated erythrocyte sedimentation rate, and extranodal involvement. One-third had bulky disease.

Treatment with pembrolizumab led to a CMR in 11 patients and deep responses that narrowly missed the criteria for CMR in 8 patients.[3] The latter finding prompted Allen and colleagues to add a new response category, near-CMR, which they defined as a reduction in metabolic tumor volume of 90% or more. There was no correlation between the disease stage or Epstein-Barr virus–encoded RNA status and the depth of response to pembrolizumab. There was a statistically significant association between bulky disease and near-CMR (P=.042).

With extended follow-up of 33.1 months, the rates of PFS and overall survival (OS) were 100%.[3] No patients relapsed, died, or discontinued treatment. The decline in metabolic tumor volume is shown in Figure 2.

FISH analysis was performed in 28 of 30 patients.[3] All of these patients had some degree of chromosome 9p24.1 alteration, with half of patients expressing a gain in copy number and the remainder expressing amplification.[3] Immunohistochemistry was performed in 29 of 30 patients to investigate PD-1 pathway markers, including PD-L1, PD-L2, and phosphor-STAT3. The 9p24.1 amplicon also includes Janus kinase (JAK) 2, which further augments JAK/STAT signaling and PD-L1 expression.[4] H scores were calculated by combining the staining intensity from a range of 0 to 3 multiplied by the percentage of positive tumor cells (0%-100%), for a total score of 0 to 300. The median H scores were 215 (range, 20-300) for PD-L1, 20 (range, 0-180) for PD-L2, and 300 (range 60-300) for STAT3. There was no correlation between these PD-1 pathway markers and metabolic response to pembrolizumab monotherapy. Furthermore, there was no correlation between PD-L1 or PD-L2 H scores when analyzed by terciles.

The investigators concluded that previously untreated classical Hodgkin lymphoma is sensitive to treatment with sequential pembrolizumab and AVD. PD-1 pathway markers did not correlate to the depth of response to pembrolizumab. Therefore, treatment with pembrolizumab could be successful even in patients with low levels of PD-L1 expression. An upcoming study will investigate sequential pembrolizumab and AVD in a larger cohort of patients with early-stage or advanced-stage classical Hodgkin lymphoma (KEYNOTE-C11).[5] The study will employ T-cell receptor sequencing to assess T-cell diversity and peripheral blood flow cytometry to identify T-cell specific responses to pembrolizumab.

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Novel Salvage Regimens Lead to Better Response and Survival in Relapsed/Refractory Classic Hodgkin Lymphoma After Autologous Stem Cell Transplant

Desai and colleagues reported on a large retrospective cohort study comparing novel and conventional salvage therapies among 853 patients with relapsed or refractory classical Hodgkin lymphoma who underwent autologous stem cell transplant (ASCT) at 12 participating institutions.[1] The patients' median age was 33 years, and approximately one-third had advanced-stage disease (30%), extranodal disease (32%), or early relapse within a year of treatment (36%).[1] All patients had received at least 1 salvage therapy prior to ASCT, with 342 (40%) receiving 2 or more lines of salvage treatment.

A reference group consisted of patients who received platinum-based chemotherapy as their first salvage therapy (n=554). In this group, the ORR was 79% and the CR rate was 49%.[1] For patients who received bendamustine plus brentuximab vedotin (n=69), the ORR was 93%, with a CR rate of 79% (Figure 3). Among patients treated with brentuximab vedotin plus nivolumab (n=49), the ORR was 86%, and the rate of CR was 67%. For both of these treatments, the improvement in ORR vs the reference group was statistically significant (*P*<.001). Treatment with brentuximab vedotin alone (n=65) led to an ORR of 62% and a CR rate of 34%, which was significantly lower compared with the reference group (*P*<.001).[1] There were no significant differences in response between the reference group and patients receiving gemcitabine-based chemotherapy, checkpoint inhibitors, and other miscellaneous agents as first salvage therapy.

The predictors of response were determined after adjusting for adverse disease features (eg, the presence of B symptoms, early relapse, and primary refractory disease).[1] Treatment with bendamustine plus brentuximab vedotin was consistently associated with a higher ORR (odds ratio [OR], 3.48; *P*<.001) and CR rate (OR, 4.4; *P*<.001) compared with the reference group. Brentuximab vedotin monotherapy was associated with a lower ORR (OR, 0.4; *P*=.002) and CR rate (OR, 0.5; *P*=.03) vs the reference group. Treatment with brentuximab vedotin plus nivolumab was associated with a nonsignificant trend toward a higher ORR (OR, 2.1) and a significantly higher CR rate (OR, 2.6; *P*=.005).

The study also analyzed PFS according to the salvage therapy that patients received before ASCT. The

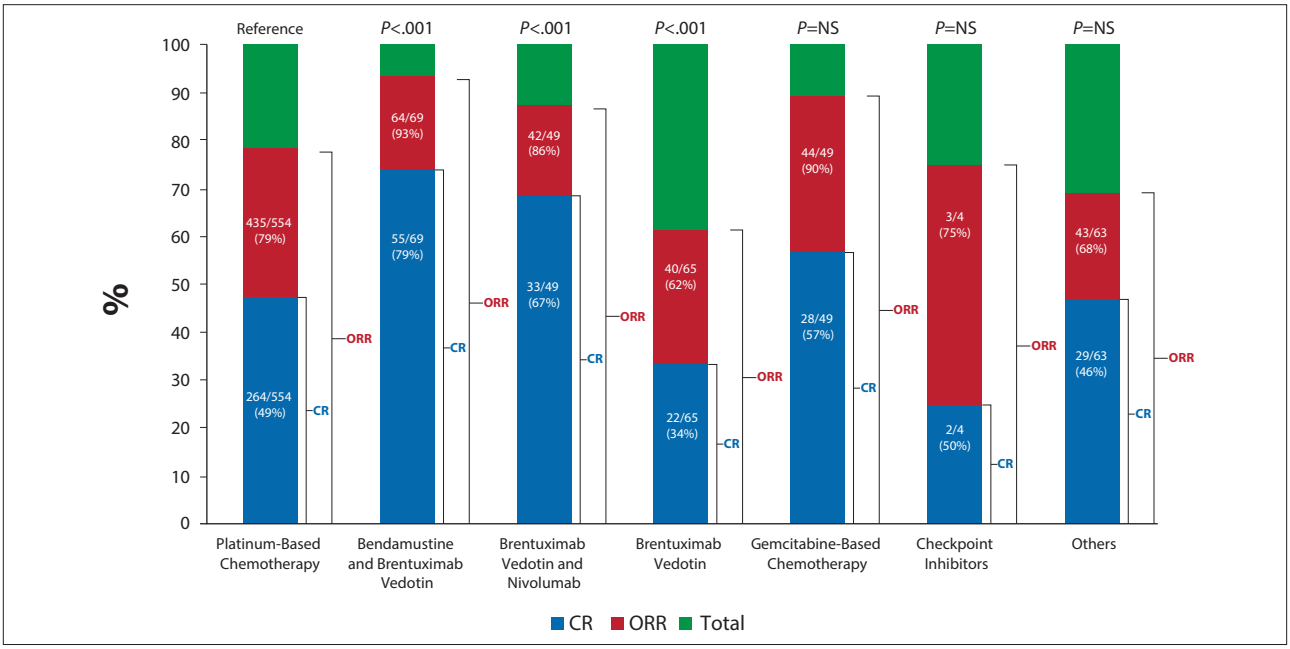

Figure 3. Response to first salvage therapy in a retrospective cohort study comparing novel and conventional salvage therapies in patients with relapsed or refractory classical Hodgkin lymphoma who underwent autologous stem cell transplant. CR, complete response; NS, not significant; ORR, objective response rate. Adapted from Desai SH et al. ASH abstract 878. *Blood*. 2021;138(suppl 1).[1]

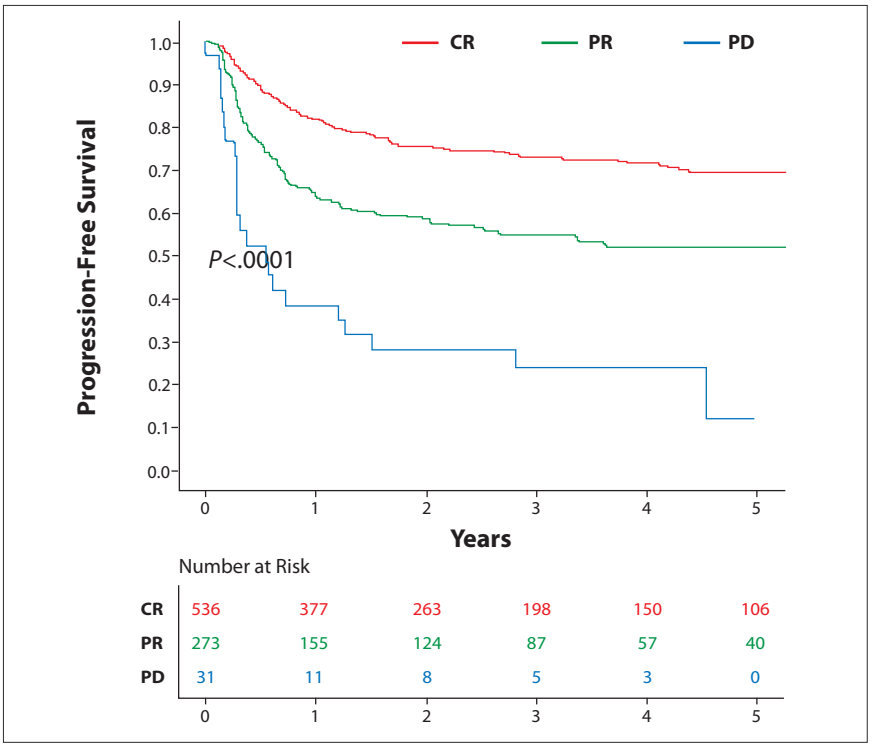

Figure 4. Survival according to pretransplant response in a retrospective cohort study comparing novel and conventional salvage therapies in patients with relapsed or refractory classical Hodgkin lymphoma. CR, complete response; PD, progressive disease; PR, partial response. Adapted from Desai SH et al. ASH abstract 878. *Blood*. 2021;138(suppl 1).[1]

rate of 2-year PFS was 65.4% for the reference group, 95.2% for brentuximab vedotin plus nivolumab, 89.7% for checkpoint inhibitors, 70.3% for other treatments, 69.3% for bendamustine plus brentuximab vedotin, 67.6% for brentuximab vedotin alone, and 62.6% for gemcitabine. The improvements with brentuximab vedotin plus nivolumab and the checkpoint inhibitors vs the reference group were statistically significant (P<.01) Differences in the rates of OS at 2 years were not statistically significant. The rate of 2-year OS was 91.8% for the reference group, 97.7% for brentuximab vedotin plus nivolumab, 100% for checkpoint inhibitor therapy, 82.5% for other treatments, 91.8% for bendamustine plus brentuximab vedotin, 94.9% for brentuximab vedotin alone, and 92.4% for gemcitabine. There was a trend toward improvement with brentuximab vedotin plus nivolumab and checkpoint inhibition.

At 2 years, survival was significantly worse among patients with a partial response (PR) or progressive disease after pretransplant salvage therapy, compared with patients with a CR.[1] The 2-year PFS was 75.4% in patients with a CR, 58.4% in those with a PR, and 27.9% in those with progressive disease. Rates of 2-year OS were 94.8%, 88.6%, and 69.0%, respectively. Patients who underwent ASCT following a PR after one line of salvage therapy had significantly worse outcomes (2-year PFS of 55.5% and 2-year OS of 86.5%) compared with patients who achieved a CR after treatment with 2 or more lines of salvage therapy prior to transplant (2-year PFS of 78.5% and 2-year OS of 97.7%; Figure 4).

ABSTRACT SUMMARY Brentuximab Vedotin as Consolidation Therapy Following Autologous Stem Cell Transplantation in Children and Adolescents With Relapsed/Refractory Hodgkin Lymphoma: A Multicenter Retrospective Analysis

Forlenza and colleagues utilized the REDCap database to perform a retrospective analysis of pediatric patients with relapsed/refractory Hodgkin lymphoma treated with brentuximab vedotin consolidation following high-dose chemotherapy and ASCT (Abstract 2465). Among 50 evaluable patients, the median time from ASCT to initiation of brentuximab vedotin was 52 days. The patients received a median of 12 cycles of brentuximab vedotin. Thirty-three patients (66%) received fewer than 16 cycles of consolidation therapy owing to AEs (n=21), patient decision (n=4), physician decision (n=4), ongoing treatment (n=3), and relapse (n=1). The most common AEs leading to discontinuation were neuropathy (67%), cytopenias (14%), and pneumonitis (10%). At a median follow-up of 2.8 years, 48 patients were alive with no evidence of disease and 2 patients were alive with disease. No deaths were reported at the time of the report. The 3-year event-free survival was 92% overall, 100% for patients with 0 to 1 risk factors, and 89% for patients with 2 or more risk factors.

The investigators concluded that, compared with conventional chemotherapy, pretransplant salvage therapy with either brentuximab vedotin plus nivolumab or checkpoint inhibitors consistently led to better survival outcomes. In addition, bendamustine plus brentuximab vedotin was associated with a higher response rate and similar posttransplant survival as reported with conventional chemotherapy. Salvage therapies with novel regimens such as brentuximab vedotin plus nivolumab and bendamustine plus brentuximab vedotin might be preferable in relapsed/refractory classical Hodgkin lymphoma.

Reference

1. Desai SH, Spinner MA, David KA, et al. Novel salvage regimens lead to better response and survival in relapsed refractory classic Hodgkin lymphoma after autologous stem cell transplant [ASH abstract 878]. *Blood*. 2021;138(suppl 1).

Effect of Brentuximab Vedotin Addition to Chemotherapy and Prognostic Factors in Patients With Relapsed/Refractory Hodgkin Lymphoma: A Large Multi-Trial Analysis Based on Individual Patient Data

Driessen and colleagues investigated whether the addition of brentuximab vedotin to salvage treatment with chemotherapy improves survival among patients with relapsed/refractory classical Hodgkin lymphoma.[1] The analysis included prospective clinical studies of classical Hodgkin lymphoma patients experiencing their first relapse or primary refractory disease (defined as the lack of CR to first-line therapy) who received brentuximab vedotin plus chemotherapy or chemotherapy alone. A total of 391 patients from 7 studies of brentuximab vedotin plus chemotherapy and 327 patients from 2 studies of chemotherapy alone were included.

The study investigators performed propensity score matching of patient characteristics to better compare PFS and OS between the cohorts.[1] The cohorts were matched according to characteristics such as primary refractory disease, stage 3/4 disease, B symptoms, extranodal disease, bulky disease, and prior treatment with bleomycin, etoposide, doxorubicin hydrochloride, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). The 3-year PFS was 74% for brentuximab vedotin plus chemotherapy vs 67% for chemotherapy alone, a difference that did not reach statistical significance (P=.13). The 3-year OS was 94% for brentuximab vedotin plus chemotherapy vs 80% for chemotherapy (P=.0002; Figure 5).

The addition of brentuximab vedotin to pretransplant salvage chemotherapy appeared to increase

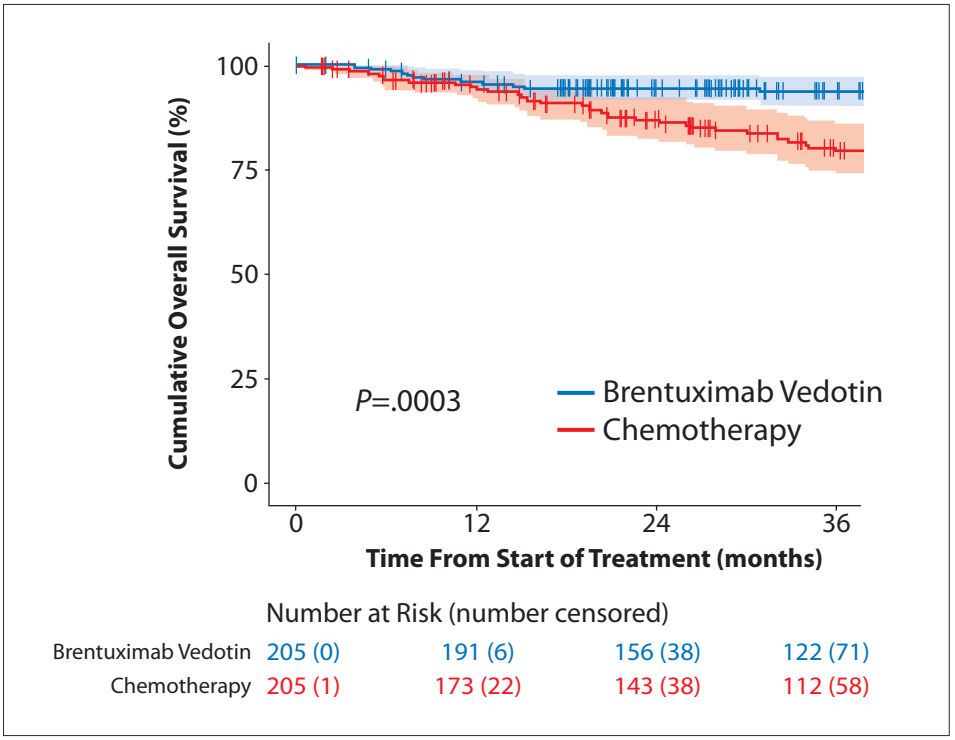

Figure 5. Overall survival at 3 years among patients treated with brentuximab vedotin plus chemotherapy or chemotherapy alone in a prospective analysis of clinical studies that enrolled patients with classical Hodgkin lymphoma experiencing their first relapse or primary refractory disease. Adapted from Driessen J et al. ASH abstract 879. *Blood*. 2021;138(suppl 1).[1]

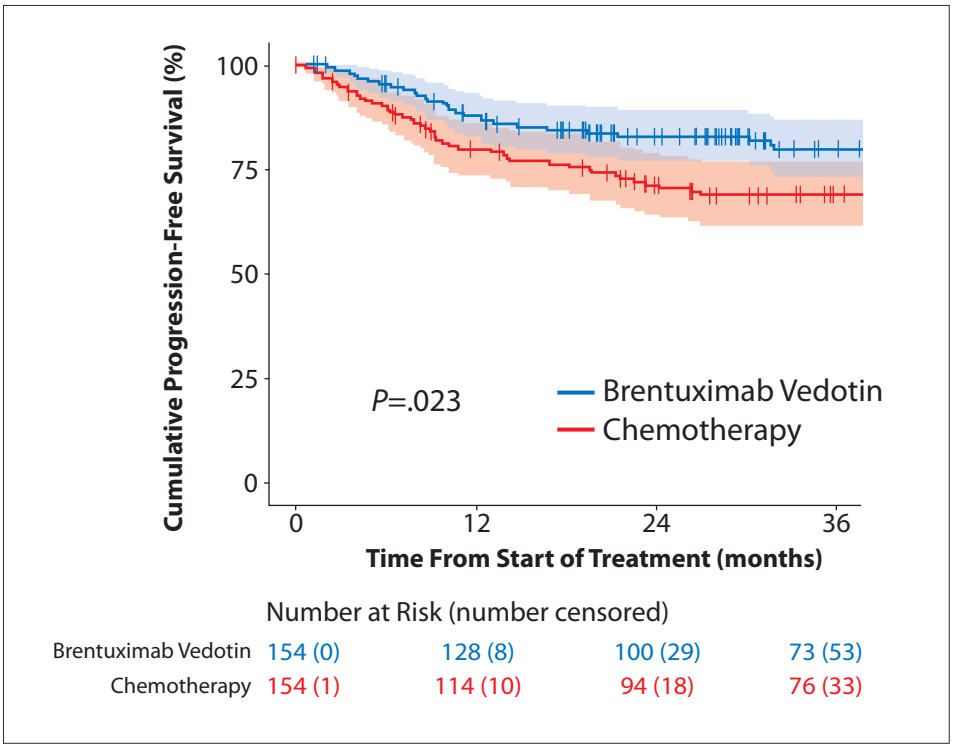

Figure 6. Progression-free survival at 3 years among patients with relapsed classical Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy or chemotherapy alone in a prospective analysis. Adapted from Driessen J et al. ASH abstract 879. *Blood.* 2021;138(suppl 1).[1]

PFS in patients with relapsed classical Hodgkin lymphoma, but not in patients with primary refractory classical Hodgkin lymphoma.[1] For relapsed patients, the 3-year PFS was 80% for brentuximab vedotin plus chemotherapy vs 69% for chemotherapy alone (*P*=.023; Figure 6). For patients with primary refractory disease, the 3-year PFS was 57% for brentuximab vedotin plus chemotherapy vs 62% for chemotherapy alone (*P*=.5). For 3-year OS, a similar benefit was observed for relapsed patients (97% vs 83%; *P*<.01), but not for patients with primary refractory disease (85% vs 72%; *P*=.17).

The study investigators also analyzed data according to differences in the salvage regimen, such as the chemotherapy agents, the administration approach (sequential or concurrent), the number of brentuximab vedotin cycles, and the cumulative dose of brentuximab vedotin.[1] The various brentuximab vedotin salvage regimens led to similar PFS rates. There was no difference in PFS between studies evaluating sequential or concurrent pretransplant salvage regimens, as long as patients achieved a CMR prior to ASCT. This finding suggests that a sequential treatment approach is feasible and could help avoid toxicities.

The 3-year PFS was significantly better in patients with a CMR (n=349) than in patients with a PR (n=67). Response rates according to PET/CT were 79% vs 58%, respectively (HR, 2.48; *P*<.0001).[1] Logistic regression showed a significantly higher CMR rate for patients treated with brentuximab vedotin plus chemotherapy vs those who received ifosfamide, carboplatin, and etoposide (ICE; 73% vs 61%; OR, 2.55; *P*<.001). However, there was no difference in the CMR rate among those treated with brentuximab vedotin plus chemotherapy vs those in the chemotherapy cohort who received ICE plus gemcitabine, vinorelbine, and doxorubicin (83% vs 84%; OR, 0.73; *P*=.34). Patients with primary refractory disease or B symptoms had a significantly lower chance of achieving a CMR.

In the overall cohort, prognostic factors associated with a significantly higher probability of progression included primary refractory disease (HR, 2.76), B symptoms (HR, 1.90), stage 3/4 disease (HR, 2.31), and bulky disease (HR, 1.52). An evaluation of studies with post-ASCT PET data showed that a positive PET scan (HR, 2.61), primary refractory disease (HR, 2.61), B symptoms (HR, 1.63), and stage 3/4 disease (HR, 2.80) were significantly associated with a higher chance of progression.

The investigators concluded that this patient-level analysis confirms the strong prognostic value of pretransplant CMR rates in predicting PFS outcomes. The presence of B symptoms, late-stage disease, and primary refractory disease appear to be prognostic indicators associated with higher probability of progression.

Reference

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Pembrolizumab Added to ICE Chemotherapy Results in High Complete Metabolic Response Rates in Relapsed/Refractory Classic Hodgkin Lymphoma: A Multi-Institutional Phase 2 Trial

The ICE regimen is associated with CR rates of approximately 50%.[1] Pembrolizumab is a checkpoint inhibitor currently approved by the US Food and Drug Administration for the treatment of relapsed/refractory Hodgkin lymphoma. Bryan and colleagues evaluated whether the combination of pembrolizumab plus ICE would improve the CMR rate prior to ASCT.[1] The primary endpoint of this phase 2 trial, CMR by PET/CT assessment, was powered to improve the historical CMR rate seen with ICE alone by 20%. The trial enrolled 43 adults with relapsed/refractory classical Hodgkin lymphoma who were deemed medically fit for ASCT and had received no more than 2 prior regimens. (The trial excluded patients previously treated with PD-1 inhibitors.) The patients received two 21-day cycles of pembrolizumab plus ICE. Peripheral blood stem cells were harvested, and patients received 1 cycle of pembrolizumab monotherapy, at which point CMR was determined by PET/CT. Patients with a Deauville score of 3 or lower could receive an additional cycle of pembrolizumab plus ICE prior to ASCT. Patients with a Deauville score higher than 3 were treated off-study at the discretion of the treating physician.

Among the 37 evaluable patients, the median age was 37 years (range, 19 to 70). Fourteen patients (39%) had primary refractory disease, 12 (32%) experienced disease relapse within a year, and 6 (16%) had bulky disease (>10 cm).[1] The patients therefore represented a high-risk population.

The CR rate was 86.5%. The Deauville score was 3 or lower in 80% of patients. Two patients with Deauville scores higher than 3 had follow-up biopsies that confirmed noncaseating granuloma and cells positive for the Epstein-Barr virus, both without evidence of lymphoma. Most patients (95%) underwent ASCT. Five patients (14%) received an optional third cycle of pembrolizumab plus ICE. The 2-year PFS was 88.2% (Figure 7), and the 2-year OS was 95.1% (Figure 8).

Stem cell mobilization/collection and engraftment were assessed as secondary endpoints in 40 patients.[1] The patients underwent a mean of 1.6 (range, 1-7) apheresis sessions, during which a mean of 9.6 million cells/kg (range, 1.6-46.1) were collected. Recovery of the absolute neutrophil

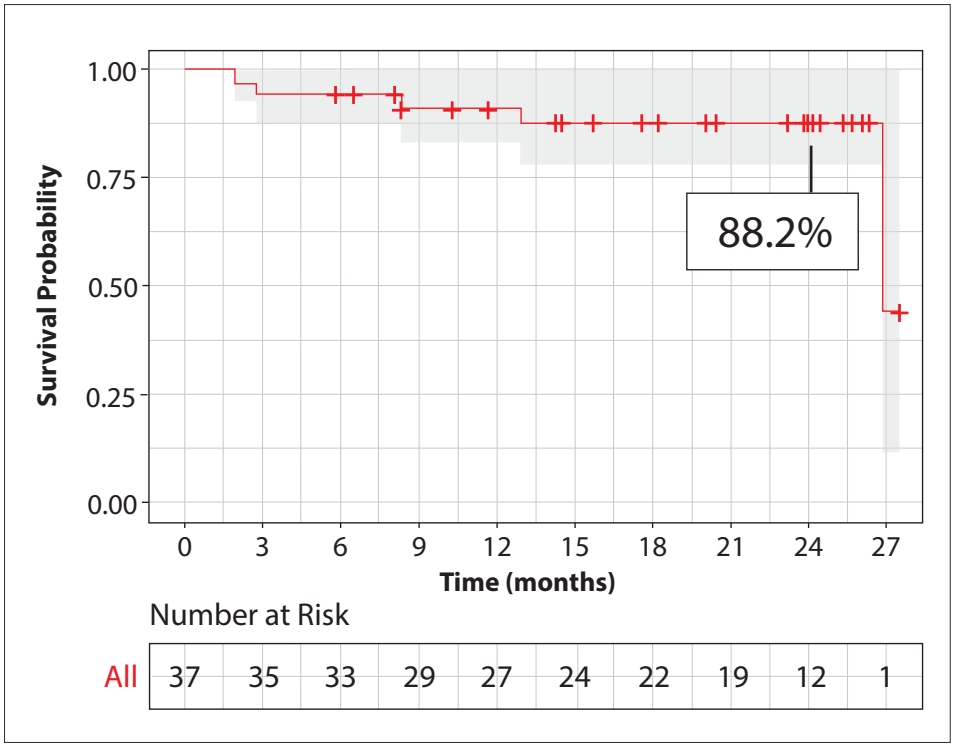

Figure 7. Progression-free survival in a phase 2 trial of pembrolizumab plus ICE in patients with relapsed/refractory classical Hodgkin lymphoma. ICE, ifosfamide, carboplatin, and etoposide. Adapted from Bryan LJ et al. ASH abstract 229. *Blood*. 2021;138(suppl 1).[1]

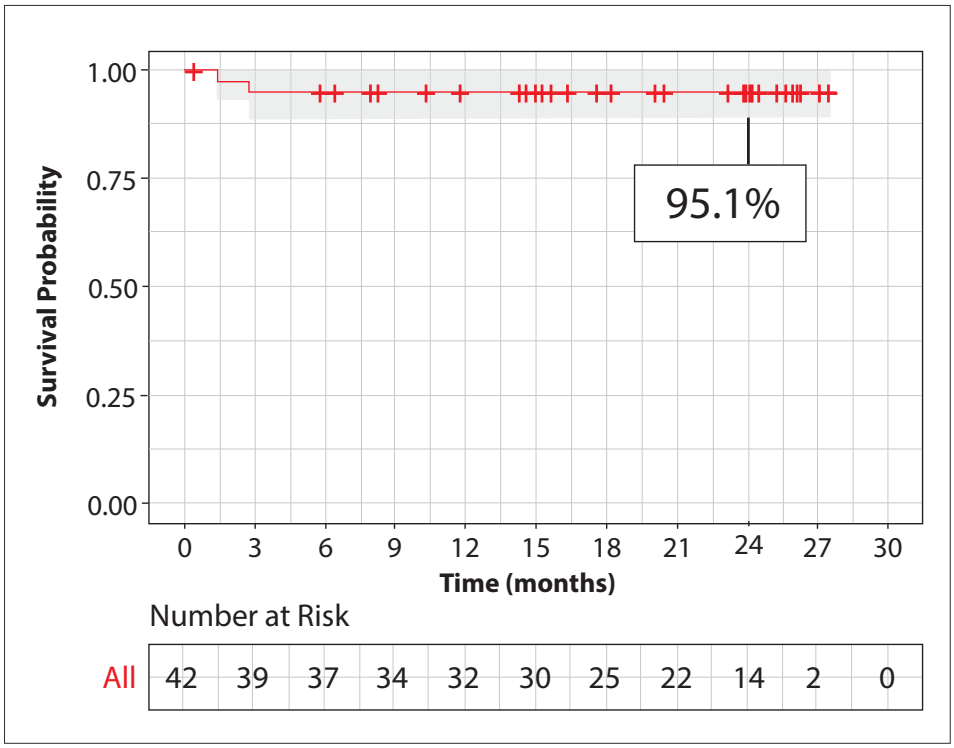

Figure 8. Overall survival in a phase 2 trial of pembrolizumab plus ICE in patients with relapsed/refractory classical Hodgkin lymphoma. ICE, ifosfamide, carboplatin, and etoposide. Adapted from Bryan LJ et al. ASH abstract 229. *Blood*. 2021;138(suppl 1).[1]

count occurred after an average of 11 days (range, 9-24). The platelet count recovered after an average of 12 days (range, 8 to 23).

The most common grade 3/4 hematologic toxicities were thrombocytopenia (93%), anemia (76%), and febrile neutropenia (29%).[1] The most common grade 3/4 nonhematologic toxicities were hypokalemia (36%), hypophosphatemia (26%), and oral mucositis (24%). There was 1 case of acute respiratory distress syndrome attributed to pembrolizumab, which occurred following ASCT and led to fatal engraftment syndrome.

Reference

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Pembrolizumab Plus Vorinostat Induces Responses in Patients With Hodgkin Lymphoma Who Are Refractory to Prior PD-1 Blockade

Combination regimens containing anti–PD-1 agents may help patients with relapsed or refractory classical Hodgkin lymphoma overcome resistance to PD-1 blockade.[1] Herrera and colleagues investigated treatment with the histone deacetylase inhibitor vorinostat in combination with pembrolizumab.[1] The phase 1 trial enrolled patients with refractory disease, defined as those with stable disease or progressive disease as best response to therapy, or progressive disease during anti–PD-1 monotherapy. The study design encompassed dose escalation (n=12) and dose expansion (n=30) in a patient cohort of mixed histologies (classical Hodgkin lymphoma, follicular lymphoma, and diffuse B-cell lymphoma). Herrera and colleagues presented the findings for the classical Hodgkin lymphoma cohort (n=32), most of whom received treatment at dose level 2 (pembrolizumab at 200 mg on day 1 and vorinostat at 200 mg bid on days 1 to 5 and days 8 to 15 of each 21-day cycle).

Most of the patients with classical Hodgkin lymphoma had primary refractory disease (69%) or advanced disease (stage 3/4, 75%), and were relatively heavily pretreated (median, 4 prior therapies).[1] Two-thirds of patients were refractory to brentuximab vedotin (n=21), and 56% (n=18) were refractory to anti–PD-1 therapy. Patients received a median of 8.5 cycles of therapy (range, 1-36). One patient

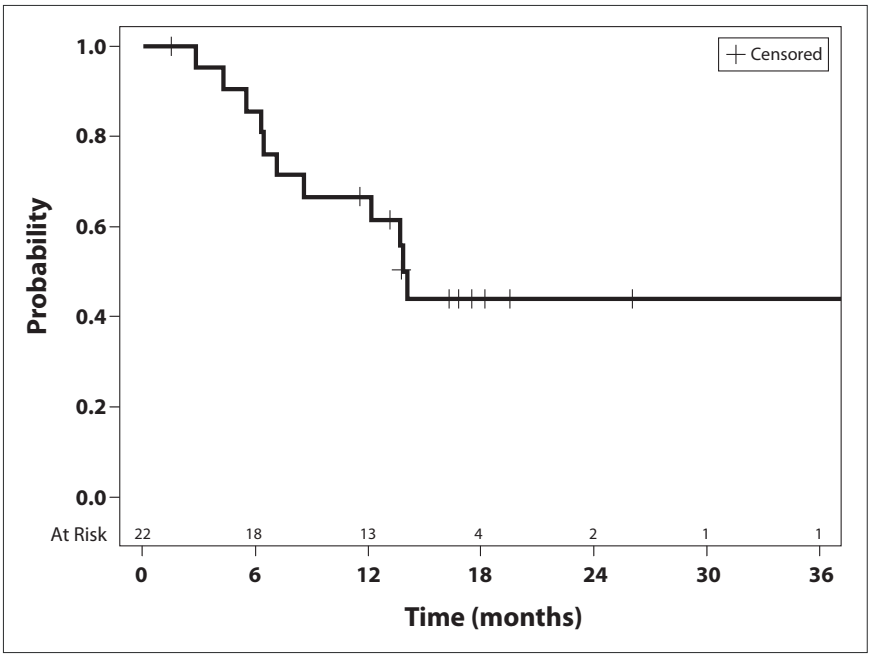

Figure 9. Duration of response among patients with relapsed/refractory classical Hodgkin lymphoma who received pembrolizumab plus vorinostat in a phase 1 trial. Adapted from Herrera AF et al. ASH abstract 234. *Blood*. 2021;138(suppl 1).[1]

required a vorinostat dose reduction owing to neutropenia. Treatment was ongoing in 8 patients at the time of the data cutoff. Reasons for treatment discontinuation included disease progression (41%), transplant (19%), patient preference (6%), completion of 2 years of therapy (6%), and AEs (3%). The most common treatment-related AEs were hypertension, fatigue, nausea, and diarrhea. Four patients experienced grade 1/2 thyroiditis, 2 patients had grade 1 rash, and 1 patient had grade 3 esophagitis/duodenitis that resolved with corticosteroids and allowed the patient to resume treatment and complete 34 cycles of therapy.

The ORR was 75% and the CR rate was 34% in the overall classical Hodgkin lymphoma cohort.[1] The ORR rates were 100% in patients who had not received anti–PD-1 therapy, 86% of patients sensitive to anti–PD-1 therapy, and 61% in patients refractory to anti–PD-1 therapy. The rates of CR were 57%, 71%, and 11%, respectively. The ORR was 67% in a subgroup of 12 patients who received anti–PD-1 therapy as their most recent prior treatment. There was a median delay of 35 days from progressive disease during prior anti–PD-1 therapy and the start of pembrolizumab plus vorinostat.

After a median follow-up of 19.8 months, the 1-year duration of response was 67% (Figure 9). The duration of response was 77% in patients who were naive or sensitive to anti–PD-1 therapy vs 50% in those who were refractory to anti–PD-1 therapy.[1] The rates of PFS at 1 year were 47% in the overall classical Hodgkin lymphoma cohort, 71% in patients naive or sensitive to anti–PD-1 therapy, and 24% in anti–PD-1 refractory patients. The 1-year rate of OS was 93%. The median OS had not been reached at the time of the report.

Reference

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Concurrent Pembrolizumab With AVD for Untreated Classical Hodgkin Lymphoma

Several new drugs approved for classical Hodgkin lymphoma, including PD-1 inhibitors, are active among patients with relapsed/refractory disease, but do not appear to be curative in most cases.[1] Lynch and colleagues evaluated the addition of pembrolizumab to AVD (≥2 cycles) in a single-arm, single-center, investigator-initiated pilot study. The trial enrolled 30 patients. Their median age was 33 years (range, 18-69). Most patients (60%) had advanced-stage disease. Extranodal involvement was reported in 37%. An International Prognostic Score (IPS) of 4 to 7 was noted in 28%. An interim PET scan was performed after the second cycle of treatment, and patients could receive up to 4 additional cycles of combination treatment followed by an additional PET

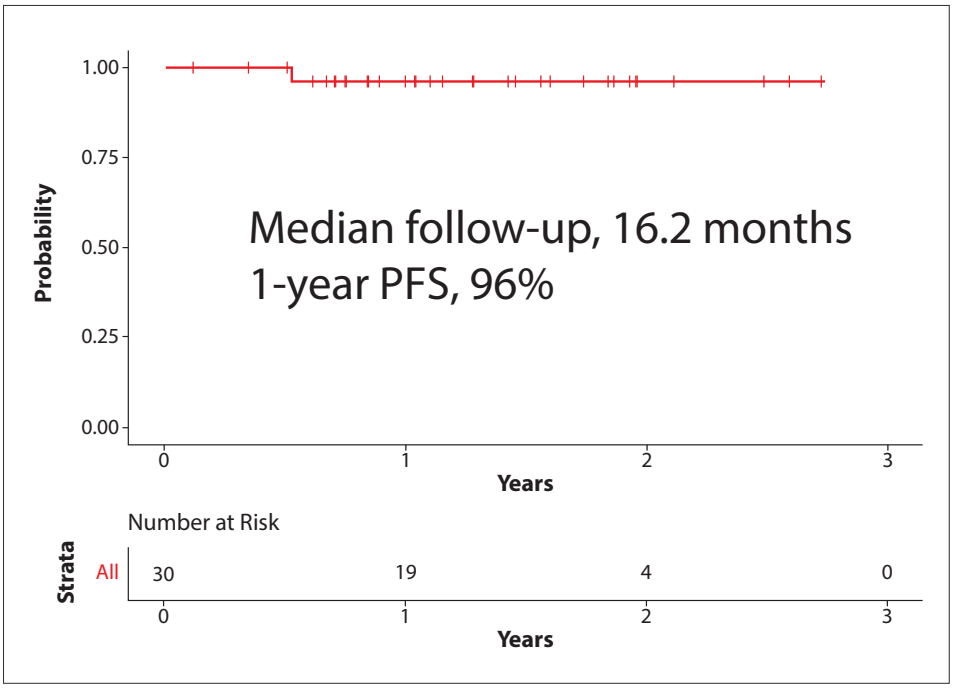

Figure 10. Progression-free survival among patients with classical Hodgkin lymphoma treated with concurrent pembrolizumab plus AVD in a pilot study. AVD, doxorubicin, vinblastine, and dacarbazine; PFS, progression-free survival. Adapted from Lynch RC et al. ASH abstract 233. *Blood*. 2021;138(suppl 1).[1]

scan. Among 30 enrolled patients, 29 completed at least 2 cycles of therapy and underwent the interim PET scan.[1] Most patients (73%) received 6 cycles of therapy. Fewer cycles were administered based on factors such as disease stage, investigator preference, or toxicity.

There were no deaths from any cause, including during the long-term follow-up period. The ORR was 100%, including a CR rate of 66%, based on the interim PET scan after the second cycle.[1] There were no treatment delays lasting 21 days or longer during the first 2 cycles of treatment. After the interim PET scan, 1 patient who developed grade 3 transaminitis discontinued study treatment and switched to brentuximab vedotin plus AVD. Three early-stage patients achieved a CR and did not receive additional pembrolizumab plus AVD beyond the first 2 cycles. A total of 25 patients received 2 to 4 additional cycles of pembrolizumab plus AVD. At the end of treatment, the CR rate was 81%. Among the 5 patients with residual ^{18}F-fluorodeoxyglucose uptake at the end of the study, only 1 developed biopsy-proven progressive disease.

After a median follow-up of 16.2 months, the 1-year rate of PFS was 96% (Figure 10). The rate of 1-year OS was 100%. No cases of progressive disease were reported among the patients who omitted a dose of pembrolizumab, interrupted study treatment, or permanently discontinued study treatment owing to an AE. Correlative studies performed in a limited sample of patients suggested that circulating tumor DNA might help identify false-negative and false-positive PET scans.

Grade 3/4 nonhematologic AEs included febrile neutropenia (17%), hyponatremia (10%), and syncope (10%).[1] One patient developed a grade 4 large bowel obstruction and abscess, but there was no evidence of colitis. Six patients (20%) missed at least 1 dose of pembrolizumab, mostly owing to grade 2 or higher transaminitis, which was transient and reversible. Grade 3 or 4 immune-related AEs, such as elevated levels of alanine aminotransferase, elevated levels of aspartate transaminase, and rash, were successfully managed with protocol-specified therapy, including corticosteroids.

Lynch and colleagues concluded that pembrolizumab plus AVD without a PD-1 inhibitor lead-in represents a well-tolerated and effective backbone that should be further evaluated in patients with untreated classical Hodgkin lymphoma. Although transaminitis was more common than typically seen with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), this AE was reversible and did not appear to impact treatment efficacy. Positive interim PET scans with this regimen were not associated with a high risk of disease recurrence. Only 20% of patients with a positive end-of-treatment PET scan developed recurrent lymphoma, highlighting the need for improved tools for response assessment in patients with classical Hodgkin lymphoma receiving PD-1 inhibitor–based therapy.

Reference

1. Lynch RC, Ujjani CS, Poh C, et al. Concurrent pembrolizumab with AVD for untreated classical Hodgkin lymphoma [ASH abstract 233]. *Blood*. 2021;138(suppl 1).

Real-World Escalated BEACOPDac Delivers Similar Outcomes to Escalated BEACOPP and Superior Outcomes to Response-Adapted ABVD, While Potentially Reducing Toxicity Compared With Escalated BEACOPP

Researchers in Europe are investigating a modified escalated BEACOPP regimen, in which oral procarbazine is replaced with intravenous dacarbazine (250 mg/m^2 on days 2-3). The regimen is referred to as eBPDac. The modification aims to reduce hematopoietic stem cell and gonadal toxicity. To date, there are limited published data for this regimen. Santarsieri and colleagues collected real-world data on 225 patients who received eBPDac as first-line treatment for advanced Hodgkin lymphoma at 20 centers in France, Ireland, and the United Kingdom.[1] Survival outcomes were compared with 2073 patients treated with escalated BEACOPP in the HD18 trial[2] and 1088 patients who received this regimen in the RATHL trial.[3,4]

The patients treated with eBPDac were a median age of 26 years, compared with 35 years for patients in the HD18 trial and 31 years for those in the RATHL study.[1] Disease risk was higher among patients treated with eBPDac vs those in the other trials. The IPS was 4 or higher in 36% of patients in the eBPDac group vs 16% in the HD18 group (P<.001). The IPS was 3 or higher in 65% of patients in the eBPDac group vs 33% in the RATHL group. Among the 225 patients who began treatment with eBPDac, 77% achieved an interim PET Deauville score of 3 or lower, which was similar to the rates observed in the HD18 trial (76%) and the RATHL (84%) trial.

After a median follow-up of 22.1 months, 212 of the 225 eBPDac patients were alive and in remission.[1] One patient had primary refractory disease, 10 relapsed, and 2 patients died. Neither of the deaths were related to lymphoma. At 22 months, the rate of PFS was 94.9% among eBPDac patients. This finding is similar to the 3-year PFS in the HD18 study (92.3%) and superior to the 5-year PFS in the RATHL study (81.4%). The difference between eBPDac and RATHL was most evident among patients with an IPS of 3 or higher. Similar OS rates were observed for all 3 regimens, with a 22-month OS estimate of 98.9% in the eBPDac cohort.

Toxicity outcomes were compared between eBPDac patients and 58 real-world patients who received escalated BEACOPP at the same 20 treatment centers.[1] Comparisons were made throughout the first 4 cycles only. Patients treated with escalated BEACOPP or eBPDac were well matched, with no significant differences in age, sex, disease stage, or IPS. There was no significant difference in levels of alanine aminotransferase at day 8 between the groups. The mean day 8 neutrophil count tended to be lower with eBPDac vs escalated BEACOPP (2.04 × 10^9/L vs 2.45 × 10^9/L; P=.072) with granulocyte colony–stimulating factor (G-CSF) administered on day 9. However, the neutrophil count increased to 6.48 × 10^9/L in eBPDac patients who received G-CSF from day 4. Patients treated with eBPDac required fewer red blood cell transfusions (mean, 1.79 vs 4.19; P<.0001) and fewer nonelective days of inpatient care (mean, 3.35 vs 5.84 days; P=.022) compared with patients who received escalated BEACOPP.

Among women ages 35 years and younger, menstrual periods returned in all those treated with eBPDac (n=39) vs 93.9% of those treated with escalated BEACOPP (P=.051).[1] In patients treated with eBPDac, menstrual periods tended to resume more quickly. However, this could reflect the

ABSTRACT SUMMARY Nivolumab First-Line Therapy for Elderly, Frail Hodgkin Lymphoma Patients: NIVINIHO, a LYSA Phase 2 Study

The phase 2 NIVINIHO trial is evaluating nivolumab for the first-line treatment of elderly, frail patients with classical Hodgkin lymphoma (Abstract 232). The presentation provided data for 64 patients in the full analysis/safety set and 56 patients in the efficacy set. The trial did not reach its prespecified primary endpoint, with a CMR rate of 28.5% at the end of study treatment. The rate of partial metabolic response was 17.9%. Progressive metabolic disease was reported in 35.7%. Nivolumab monotherapy led to an ORR of 51.8% at the end of induction, including CMRs in 9 patients (16.1%). Five patients treated with nivolumab monotherapy still had a CMR at the end of the study. At a median follow-up of 24.4 months, the median PFS and event-free survival were both estimated at 9.8 months. The median OS was not reached. The rate of OS at 2 years was estimated at 78.6%. Two deaths occurred during the induction phase (with 1 AE of special interest), but none occurred during the consolidation phase. Toxicities in the NIVINIHO study were comparable with other chemotherapeutic strategies used in elderly, frail patients with classical Hodgkin lymphoma.

higher mean number of chemotherapy cycles completed by patients receiving escalated BEACOPP (6 vs 4 cycles). Preliminary data analysis of sperm concentrations indicated normal levels in male patients treated with eBPDac at more than 2 years after completion of chemotherapy.

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Highlights in Hodgkin Lymphoma From the 63rd American Society of Hematology Annual Meeting and Exposition: Commentary

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Presentations in Hodgkin lymphoma at the 63rd American Society of Hematology (ASH) annual meeting echoed the issues that have arisen throughout my clinical practice in the past year. There is interest in finding novel up-front strategies, as well as regimens that exclude certain chemotherapies, such as bleomycin and/or anthracycline. There are patients who cannot receive these chemotherapies and who would benefit from alternative treatment strategies. The question of how to optimize salvage therapy was addressed by several prospective and retrospective studies. Another area of interest is the management of patients who have already received standard and novel therapies, such as transplant and checkpoint inhibitors.

Novel Up-Front Treatment Strategies

The single-arm, multipart phase 2 SGN35-027 trial is evaluating brentuximab vedotin in combination with nivolumab, doxorubicin, and dacarbazine in patients with classical Hodgkin lymphoma, at various stages of disease. Dr Hun Lee presented results from part B, which evaluated this regimen in patients with stage I or II, bulky mediastinal disease and in patients with advanced-stage disease.[1] This interesting trial utilizes 2 novel drugs and excludes 2 of the standard chemotherapies, including bleomycin. The regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is a traditional treatment for Hodgkin lymphoma and remains a standard of care. Treatment with bleomycin can be a concern for older patients and those who smoke or have lung disease. Dr Lee provided preliminary results of part B. After cycle 2, the overall response rate was high, at 96%, and the rate of complete remission (CR) was 74%. By the end of treatment, the CR rate increased to 88%. It is promising to see alternatives to the traditional chemotherapy approach, in which novel agents replace components of standard regimens while maintaining high efficacy.

Part C of the SGN35-027 trial enrolled a cohort of patients with early-stage, nonbulky disease. At the 2021 ASH meeting, a poster described the trial design; no data were provided.[2] I have a patient at the Cleveland Clinic who is enrolled in part C of the trial. The patient is doing well and is in a CR following completion of therapy. In summary, the combination of brentuximab vedotin plus nivolumab, doxorubicin, and dacarbazine appears safe and promising in terms of efficacy, while avoiding the risk of pulmonary toxicity from bleomycin. Long-term follow-up is needed.

Dr Pamela Allen presented long-term results of a study that evaluated frontline treatment with pembrolizumab followed by doxorubicin, vinblastine, and dacarbazine (AVD).[3,4] In addition to the impressive responses, the presentation provided interesting data from correlative studies. As a fellow in oncology, I remember a nuance raised by specialists in lung cancer concerning the level of programmed death ligand 1 (PD-L1) expression that would allow successful treatment with

a checkpoint inhibitor. The analysis by Dr Allen showed high response rates even among patients with low levels of PD-L1/PD-L2 expression. All patients were still alive and without progression after an extended follow-up of 33.1 months. The rates of progression-free survival (PFS) and overall survival were 100%.

A single-arm pilot study evaluated pembrolizumab administered concurrently with AVD (as opposed to the prior study, which evaluated sequential administration) in patients with untreated classical Hodgkin lymphoma.[5] Most of the patients in this study (60%) had advanced-stage disease. A secondary endpoint was CR according to positron emission tomography (PET) after 2 cycles of treatment. A high percentage of patients (66%) were PET2-negative. An interesting finding was that none of these PET2-positive patients have developed progressive disease to date. Historically, PET2 has been an important prognostic sign of progression among patients who are receiving chemotherapy-based strategies (without novel agents). The observation that PET2-positive patients have not developed progressive disease raises questions about the utility of PET scans in patients receiving checkpoint inhibitors. In other studies, biopsies of patients with residual disease according to PET have revealed that the finding does not always reflect the presence of lymphoma.[6,7] The study showed an impressive end-of-therapy CR rate of 81%. At the end of treatment, 5 patients had residual ^{18}F-fluorodeoxyglucose (FDG) uptake on their PET scan, but only 1 had developed recurrent lymphoma. The other patients have undergone serial scans with or without biopsies without confirmed disease progression. Further research will be needed to explore this issue because the use of checkpoint inhibitors is becoming more common. The 1-year rate of PFS was 96%. Therefore, both of these small studies of pembrolizumab plus AVD showed impressive efficacy warranting further investigation.

A prospective phase 2 trial evaluated nivolumab with or without vinblastine as first-line therapy in older, frail patients with classical Hodgkin lymphoma.[8] Vinblastine was added to nivolumab during the consolidation phase for patients with a partial metabolic response or stable disease at the completion of induction therapy. The trial used the Cumulative Illness Rating Score for Geriatrics to determine frailty and therefore inclusion of patients. This patient population is difficult to treat. Historically, outcomes are worse for older patients based on factors such as disease biology, ability to tolerate treatment, and treatment-related mortality and morbidity. I commend the investigators for studying treatment in this group of patients, who are certainly seen in clinical practice and who require novel and tolerable strategies. The rates of grade 3 or higher adverse events were high, at 21.9% during the induction phase and 47.1% during the consolidation phase. An adverse event led to discontinuation of nivolumab in 17.2% of patients during the induction phase and 23.5% of patients during the consolidation phase. Some patients also discontinued treatment with vinblastine. Among the 56 patients in the efficacy population, only 34% completed treatment. These findings highlight the difficulties in treating this patient population, who have a higher incidence of treatment-related morbidity, whether with traditional chemotherapy or, in this case, even novel agents. At the end of induction treatment, only 16.1% of patients were in a complete metabolic response (CMR). The results of this study stress that these patients still represent an unmet need in terms of treatments that are safe, tolerable, and effective.

Dr Tycel Phillips presented an oncology simulation model to estimate the 10-year PFS of patients treated with up-front brentuximab vedotin plus AVD.[9] I would encourage readers to review the recently published 5-year updated data from the ECHELON-1 trial,[10] which continued to show an improvement in PFS for brentuximab vedotin plus AVD compared with ABVD. This update also highlighted some important safety signals, such as improvement in neuropathy among patients treated with brentuximab vedotin. The simulation model shows ongoing durable PFS with brentuximab vedotin plus AVD, which may decrease the need for salvage therapies, including stem cell transplant.

Salvage Regimens

Dr Julia Driessen presented data from a pooled analysis that evaluated the effect of adding brentuximab vedotin to chemotherapy as salvage therapy.[11] The patients received treatment in prospective clinical trials. The investigators performed propensity score matching to compare treatment with brentuximab vedotin plus chemotherapy vs chemotherapy alone. The 3-year PFS rate was 74% with brentuximab vedotin plus chemotherapy vs 67% with chemotherapy alone, but this difference did not reach statistical significance (P=.13). The difference in overall survival was significant, at 94% vs 80%, respectively (P=.0003). I agree with an observation from the study investigators, who noted that the improvement in overall survival likely reflects the recent use of novel treatments; for instance, many of the patients treated in the chemotherapy-only arm were likely treated before checkpoint inhibitors were available.

An interesting subgroup analysis found that the addition of brentuximab vedotin to chemotherapy improved outcome among patients with relapsed disease, but not in those with primary refractory disease.[11] There is a concern that patients with primary refractory disease might be inherently refractory to chemotherapy. It makes sense that these patients would not benefit from brentuximab vedotin plus chemotherapy, but rather may need a more

novel approach, such as a checkpoint inhibitor. Another interesting finding from this study was when they looked at the remission rates pretransplant, they found that pretransplant PET had a very high prognostic value, confirming results reported in multiple other studies.[12-17] Among patients in CMR, PFS was similarly high, regardless of the salvage regimen. The rate of 3-year PFS was 79% among patients with a CMR and 58% among those with a partial response.

A retrospective analysis examined novel salvage regimens among relapsed/refractory patients undergoing autologous stem cell transplant.[18] The trial enrolled 853 patients from 12 centers. The study found that brentuximab vedotin plus nivolumab led to a higher rate of CR and better PFS after autologous stem cell transplant compared with brentuximab vedotin plus bendamustine, brentuximab vedotin alone, and platinum-based therapies. The rate of 2-year PFS according to the therapy received before autologous stem cell transplant was 95.2% with brentuximab vedotin plus nivolumab, 89.7% with checkpoint inhibitors, 67.6% with brentuximab vedotin alone, and 62.6% with gemcitabine-based chemotherapy. Interestingly, among patients with a CR, PFS was better with brentuximab vedotin plus nivolumab vs the other regimens. This finding differs from results in the previous abstract, in which CMR translated into higher rates of PFS regardless of the salvage regimen used.[11] However, this study did not specify if pretransplant CR response was based on PET/computed tomography (CT), CT, or a combination of both.

A phase 2 trial evaluated pembrolizumab plus ifosfamide, carboplatin, and etoposide (ICE) in patients with relapsed/refractory Hodgkin lymphoma.[19] This trial was similar to a previous study of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin that was presented at the 2020 ASH annual meeting and recently published.[20,21] The study had positive outcomes. Two cycles of pembrolizumab plus ICE led to a CMR in 87% of patients.[19] This finding is impressive. Historically, the rate of CR ranges from 20% to 40% among patients treated with chemotherapy only.[22-26] The study design included important safety measures regarding transplant. The addition of pembrolizumab to ICE posed no difficulties when collecting stem cells from patients. There were no issues with engraftment when the patients ultimately received their transplant.

Dr Anna Sureda presented preliminary results of a phase 2b prospective trial comparing brentuximab vedotin plus etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) vs ESHAP alone as salvage therapy, and evaluating brentuximab vedotin as consolidation therapy.[27] In the consolidation phase of the study, the investigators are evaluating whether patients with a stringent metabolic complete remission, defined as a Deauville score of 1 or 2, require autologous stem cell transplant. Similar studies define CMR as a Deauville score of 3. The stringent metabolic CR rate was 33% for brentuximab vedotin plus ESHAP vs 42% for ESHAP (P=.6). The definition of CMR likely was more stringent in this trial because the patients were receiving consolidation with brentuximab vedotin instead of an autologous stem cell transplant. Twenty-two patients have entered the brentuximab vedotin consolidation phase of the trial. This preliminary result showed that the regimen was feasible and safe, and the study will continue recruitment.

Dr Shanee Chung presented a study that evaluated the routine use of brentuximab vedotin after autologous stem cell transplant in British Columbia (where it is offered to all patients, not just those at high risk).[28] Brentuximab vedotin is being administered more frequently in up-front and salvage settings, before transplant, so my interest in use as consolidation is decreasing. There was no benefit in relapse-free survival with routine consolidative brentuximab vedotin. This study highlighted the difficulty

ABSTRACT SUMMARY: Brentuximab Vedotin Plus ESHAP (BRESHAP) Versus ESHAP as a Salvage Strategy for Patients With Primary Refractory or Relapsed Classical Hodgkin's Lymphoma: Preliminary Results From the BRESELIBET Prospective Clinical Trial

The ongoing phase 2b BRESELIBET trial is evaluating whether the addition of brentuximab vedotin to etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) will improve outcomes in patients with relapsed/refractory classical Hodgkin lymphoma (Abstract 2459). The study aims to recruit 150 patients. In a preliminary analysis of 54 patients randomly assigned to treatment, the primary endpoint of CMR was 33% in those treated with brentuximab vedotin plus ESHAP vs 42% in those treated with ESHAP alone. Treatment is ongoing in 13 patients receiving brentuximab vedotin and in 16 patients receiving ESHAP alone. Patients with a CMR were permitted to receive up to 16 cycles of brentuximab vedotin consolidation therapy. Ten patients receiving brentuximab vedotin and 12 of those receiving ESHAP proceeded to the consolidation phase, with 3 patients completing treatment. Patients received a median of 6 cycles of brentuximab vedotin (range, 1 to 16). One patient relapsed during consolidation (after 3 cycles of brentuximab vedotin). Grade 3/4 hematologic AEs occurred in 40 patients. The most common of these events were neutropenia (71% in the investigative arm vs 42% in the control arm), thrombocytopenia (0% vs 33%), and anemia (29% vs 24%).

in completing the planned number of brentuximab vedotin cycles because of peripheral neuropathy, which I have encountered in clinical practice.

Overall, these studies highlight the need to identify the best salvage therapy. It is necessary to find better treatments than traditional platinum-based chemotherapy. Obtaining a CMR prior to transplant remains an important goal. Early studies of brentuximab vedotin plus nivolumab have shown good results.[6,29] However, use of brentuximab vedotin in the up-front setting is becoming more common. We now have multiple phase 2 studies highlighting the efficacy of novel agents, such as checkpoint inhibitors, added to chemotherapy. Ultimately, to prove superiority to chemotherapy alone, a randomized phase 3 study is needed. One is being planned in the cooperative group setting.

Relapse After Transplant and Checkpoint Inhibitors

Treatment options are limited for patients who relapse after a checkpoint inhibitor before or after transplant. This area is an unmet need. There are ongoing trials of CD30 chimeric antigen receptor T-cell therapy,[30] but opportunities for enrollment are few.

Dr Veronika Bachanova presented results from a phase 1/2 study of escalated ruxolitinib and nivolumab.[31] Nivolumab was administered at a flat dose. The study population was heavily pretreated. Eighty-nine percent of patients had undergone a prior autologous stem cell transplant. All patients had received unsuccessful treatment with a checkpoint inhibitor. This small study had 19 patients, and only 16 were evaluable for response. The treatment was relatively safe. The overall response rate was 75%, including complete response rates in 19%. The main goal of this study was to establish the safety of the regimen and identify the dose of ruxolitinib.

Another phase 1 study is evaluating pembrolizumab plus vorinostat in patients with relapsed/refractory classical Hodgkin lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma. Dr Alex Herrera presented results for patients with Hodgkin lymphoma.[32] The patients were very heavily pretreated; the median number of prior therapies was 4. Many patients had refractory disease. For example, 66% of patients were refractory to brentuximab vedotin and 56% were refractory to a checkpoint inhibitor. This population is considered difficult to treat. There were only 32 evaluable patients with Hodgkin lymphoma. The overall response rate was 75%, which included complete responses in 34%. The results of these 2 studies were encouraging, particularly in comparison to non–clinical trial options listed for multiply relapsed disease in guidelines from the National Comprehensive Cancer Network, such as bendamustine, lenalidomide, and everolimus.[33] These treatments have overall response rates of approximately 53%, 19%, and 40%, respectively.[34-36] Novel combinations such as this are worth further investigation.

Conclusion

Novel drugs and combinations are changing the treatment of classical Hodgkin lymphoma in both the up-front and relapsed settings. Many promising retrospective and phase 2 studies were presented at the 2021 ASH meeting. A particular interest in how to optimize salvage therapy will hopefully lead to the fruition of a randomized trial. Sequencing of therapies will become more complex, given the incorporation of novel therapies in earlier lines of treatment. Other studies at the 2021 ASH meeting highlighted the ongoing need for regimens in older patients and those with comorbidities, as well as patients who relapse despite transplant and novel therapies.

Disclosure

Dr Winter is a member of the advisory board for Seagen.

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