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ORIGINAL RESEARCH ARTICLE

Brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine in patients with advanced-stage, classical Hodgkin lymphoma: A prespecified subgroup analysis of high-risk patients from the ECHELON-1 study

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Abstract

Approximately one-third of patients diagnosed with Hodgkin lymphoma presenting with Stage IV disease do not survive past 5 years. We present updated efficacy and safety analyses in high-risk patient subgroups, defined by Stage IV disease or

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International Prognostic Score (IPS) of 4–7, enrolled in the ECHELON-1 study that compared brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A + AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as first-line therapy after a median follow-up of 37.1 months. Among patients treated with A + AVD ($n = 664$) or ABVD ($n = 670$), 64% had Stage IV disease and 26% had an IPS of 4–7. Patients with Stage IV disease treated with A + AVD showed consistent improvements in PFS at 3 years as assessed by investigator (hazard ratio [HR], 0.723; 95% confidence interval [CI], 0.537–0.973; $p = 0.032$). Similar improvements were seen in the subgroup of patients with IPS of 4–7 (HR, 0.588; 95% CI, 0.386–0.894; $p = 0.012$). The most common adverse events (AEs) in A + AVD-treated versus ABVD-treated patients with Stage IV disease were peripheral neuropathy (67% vs. 40%) and neutropenia (71% vs. 55%); in patients with IPS of 4–7, the most common AEs were peripheral neuropathy (69% vs. 45%), neutropenia (66% vs. 55%), and febrile neutropenia (23% vs. 9%), respectively. Patients in high-risk subgroups did not experience greater AE incidence or severity than patients in the total population. This updated analysis of ECHELON-1 shows a favorable benefit-risk balance in high-risk patients.

KEYWORDS
brentuximab vedotin, ECHELON-1, high risk Hodgkin lymphoma

1 | INTRODUCTION

Despite advances in recent years, advanced-stage classical Hodgkin lymphoma (cHL) treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) relapses or becomes refractory in 25%–30% of patients.[1–3] Bleomycin, etoposide, doxorubicin hydrochloride, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) results in higher initial disease control in younger, fit patients but at the expense of significantly higher acute and late toxicity, secondary malignancies, and treatment-related mortality.[4–6] Patients with Stage IV disease have a relatively poor prognosis, with an overall survival (OS) rate of approximately 76% at 5 years.[7] The development of more-effective yet tolerable treatment options for patients with advanced-stage cHL, especially those with high-risk characteristics, is warranted.

Brentuximab vedotin (BV) is a novel antibody-drug conjugate targeting the CD30 antigen expressed on Hodgkin Reed–Sternberg cells. Across a range of trials, BV has been shown to induce durable remissions in patients with cHL who relapsed after autologous stem cell transplant. In the pivotal trial, BV treatment resulted in a complete response (CR) rate of 34% (95% confidence interval [CI], 25.2–44.4) and objective response rate of 75% (95% CI, 64.9–82.6) per independent review committee.[8] Notably, a subset of 15 patients from this study achieved complete remission and maintained their response for ≥5 years; of these, six patients received consolidative allogeneic stem cell transplant, and nine patients received no further therapy after completing BV treatment.[9] The use of BV as a consolidation treatment option for adult patients with cHL at high risk of relapse or progression following autologous hematopoietic stem cell transplant resulted in improved progression-free survival (PFS) compared with placebo.[10] In a Phase 1 dose-escalation study of BV in combination with AVD, 24 of 25 patients (96%) with newly diagnosed cHL achieved complete remission.[11] Based on these findings, a global, multicenter, open-label, randomized, phase 3 clinical study, the ECHELON-1 trial, was conducted to assess the efficacy and safety of a therapeutic combination of BV plus AVD (A + AVD) versus ABVD as first-line therapy in advanced stage (III and IV) cHL.[12]

At a median follow-up of 24.6 months, primary analyses of ECHELON-1 showed a 23% risk reduction for modified PFS (hazard ratio [HR] for progression, death, or modified progression event, 0.77; 95% CI, 0.60–0.98; $p = 0.035$) in patients receiving A + AVD, with 2-year modified PFS rates of 82.1% (95% CI, 78.8%–85.0%) in patients receiving A + AVD and 77.2% (95% CI, 73.7%–80.4%) in those receiving ABVD.[12] At the primary analysis, 28 deaths had occurred with A + AVD and 39 with ABVD (HR for interim OS, 0.72; 95% CI, 0.44–1.17; $p = 0.19$).[12]

This post hoc analysis includes the updated 3-year efficacy and safety of A + AVD compared with ABVD (data cutoff, 15 October 2018; median follow-up for PFS was 37.1 months) in a prespecified high-risk patient subgroup presenting at baseline with Stage IV disease or an International Prognostic Score (IPS) of 4–7.

2 | METHODS

2.1 | Patient eligibility and study design

Full details of the ECHELON-1 study (ClinicalTrials.gov identifier NCT01712490; EudraCT 2011-005450-60) have been published.[12,13] Briefly, we recruited patients aged ≥18 years with histologically confirmed cHL (Ann Arbor stage III or IV) who had not been previously treated with systemic chemotherapy or radiotherapy