REGULAR ARTICLE

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Association of PET4 response with outcomes of BV-CHP vs CHOP in the ECHELON-2 trial in CD30$^+$ peripheral T-cell lymphoma

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Key Points

- This post hoc analysis of ECHELON-2 evaluated the prognostic impact of PET4 on complete response rates, PFS, and OS.
- PET4-negative status was associated with improved long-term efficacy with both BV-CHP and CHOP in CD30$^+$ peripheral T-cell lymphoma.

In the phase 3 ECHELON-2 trial, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (BV-CHP) significantly improved progression-free survival (PFS) and overall survival (OS) compared with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with CD30$^+$ peripheral T-cell lymphoma, benefits that were maintained at 5 years. Interim positron emission tomography (PET) scan can be used to assess prognosis and risk-stratify patients. The prognostic value of interim PET was assessed in this post hoc exploratory analysis from ECHELON-2, evaluating interim 18F-fluorodeoxyglucose PET scans after cycle 4 (PET4) and end-of-treatment–based response, and correlated with PFS per investigator and OS. PET4 response was determined by Deauville score (scores of 1-3 were considered negative [PET4-negative] and 4-5 positive [PET4-positive]) by independent review. Overall, 452 patients were randomized 1:1 to the BV-CHP (n = 226) and CHOP (n = 226) arms. Of these, 32 in the BV-CHP arm and 41 in the CHOP arm were not evaluable for PET4. In both arms, PET4-negative status was associated with improved PFS (BV-CHP: HR, 0.36; 95% CI, 0.19-0.66; CHOP: HR, 0.26; 95% CI, 0.17-0.41) and OS (BV-CHP: HR, 0.38; 95% CI, 0.18-0.78; CHOP: HR, 0.24; 95% CI, 0.14-0.41) compared with PET4-positive status. Among patients with systemic anaplastic large cell lymphoma, PET4-negative patients had improved PFS (BV-CHP: HR, 0.28; 95% CI, 0.14-0.60; CHOP: HR, 0.31; 95% CI, 0.17-0.56) and OS (BV-CHP: HR, 0.38; 95% CI, 0.16-0.94; CHOP: HR, 0.25; 95% CI, 0.12-0.55) compared with PET4-positive patients. In this exploratory analysis, PET4-negative status by Deauville score was associated with improved long-term PFS and

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Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. More information is available at https://www.pfizer.com/science/clinical-trials/trial-data-and-results.

The full-text version of this article contains a data supplement.

OS in both the BV-CHP and CHOP arms. This trial was registered at www.ClinicalTrials.gov as #NCT01777152.

Introduction

Peripheral T-cell lymphomas (PTCLs) are uncommon, heterogeneous, and often aggressive lymphomas characterized by a high risk of relapse.[1,2] The traditional treatment approach for PTCL has been cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens, followed by optional consolidation with high-dose chemotherapy/autologous stem cell transplant (ASCT) in first remission.[3,4] However, CHOP-based chemotherapy is associated with poor progression-free survival (PFS) and overall survival (OS), particularly in those with high-risk disease, as evidenced by a high International Prognostic Index and/or a histologically aggressive subtype.[5-9] Some patients experience refractory disease with progression during or shortly after undergoing chemotherapy and are not candidates for ASCT. There is an unmet need for more effective treatment strategies in these patients.[7,9,10] There is also a need for early prognostic markers to identify patients more likely to be cured or, conversely, who are at a high risk of progression.

Brentuximab vedotin (BV) is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E.[11,12] The phase 3 ECHELON-2 trial showed that BV in combination with cyclophosphamide, doxorubicin, and prednisone (BV-CHP) in patients with $CD30^+$ PTCLs significantly improved PFS (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.53-0.91; $P = .0077$) and OS (HR, 0.72; 95% CI, 0.53-0.99; $P = .0424$) compared with CHOP, with sustained results at 5 years.[7,13] BV-CHP is US Food and Drug Administration approved for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing PTCLs, including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified. BV was also previously approved for adult patients with relapsed/refractory sALCL after failure of at least 1 previous multiagent chemotherapy regimen.[11]

In PTCL, response assessment by positron emission tomography (PET) is emerging as a valuable way to assess prognosis and risk-stratify patients.[14,15] Previous retrospective studies have shown that interim and end-of-treatment (EOT) PET scans may predict long-term outcomes.[14,16] A substudy of the UK National Cancer Research Institute phase 2 randomized CHEMO-T trial[17] comparing CHOP for previously untreated PTCL for 6 cycles with gemcitabine, cisplatin, and methylprednisolone for 4 cycles found that PET response at EOT (at least 28 days after chemotherapy) was prognostic for 2-year PFS.[16] Patients with a PET-negative (Deauville score 1-3) vs PET-positive (Deauville score 4-5) scan at EOT had a 2-year PFS of 55% and 29% (HR, 0.45; 95% CI, 0.23-0.88; $P = .021$), respectively, at a median follow-up of 27 months.[16] However, there is a need for additional prospective studies with prespecified outcomes for interim PET response. We performed a post hoc exploratory subgroup analysis of the ECHELON-2 trial evaluating the prognostic impact of an 18F-fluorodeoxyglucose (FDG) PET scan at cycle 4 (PET4) on PFS and OS.

Methods

Study design

The phase 3 ECHELON-2 trial (www.ClinicalTrials.gov identifier: NCT01777152) was a double-blind, double-dummy, randomized, placebo-controlled, active comparator study (Figure 1).[7,13] The full eligibility criteria for ECHELON-2 have been published previously.[7,13] In brief, eligible patients were aged $\geq$18 years and had previously untreated $CD30^+$ PTCL (CD30 detected in $\geq$10% of neoplastic cells by local review; when enumeration of neoplastic cells was not possible, total lymphocytes were used). Eligible histologies were anaplastic lymphoma kinase–positive sALCL with an International Prognostic Index score of $\geq$2, anaplastic lymphoma kinase–negative sALCL, PTCL not otherwise specified, angioimmunoblastic T-cell lymphoma, adult T-cell leukemia/lymphoma, enteropathy-associated T-cell lymphoma, and hepatosplenic T-cell lymphoma.[18] The study was conducted in accordance with regulatory requirements, and the protocol was approved by institutional review boards and ethics committees at individual sites. All patients provided written informed consent.

As previously described, patients were randomized 1:1 to the BV-CHP or CHOP arms and received 21-day cycles of either treatment.[7] Patients in the BV-CHP arm received BV 1.8 mg/kg, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, all administered IV on day 1 of each cycle, and prednisone 100 mg daily administered orally on days 1 through 5 of each cycle. Placebo replacement for vincristine was also administered IV in a blinded manner on day 1 of each cycle. Patients in the CHOP arm received cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (dose capped at 2 mg) administered IV on day 1 of each cycle, and prednisone 100 mg daily administered orally on days 1 through 5 of each cycle. Placebo replacement for BV was also administered IV in a blinded manner on day 1 of each cycle. The number of cycles (6 or 8) and whether to use a consolidative stem cell transplant or radiotherapy was determined by investigator discretion.

The ECHELON-2 trial included standardized 18F-FDG PET/computed tomography (CT) scans at cycle 4 and EOT, as well as assessment of treatment response, including long-term PFS per investigator and OS.[7,13] In the earlier analysis, responses were assessed based on Cheson 2007 criteria.[19] In this post hoc analysis, PET4 response was determined by Deauville score as per independent review facility response assessment using scans after cycle 4 between days 15 and 21. A Deauville score, based on visual assessment, of 1 to 3 was considered negative (PET4-negative), and a score of 4 to 5 was considered positive (PET4-positive).[20,21] EOT response was the best response after completion of study treatment and prior to long-term follow-up per the Revised Response Criteria for Malignant Lymphoma[19] by independent review facility assessment. Complete remission was

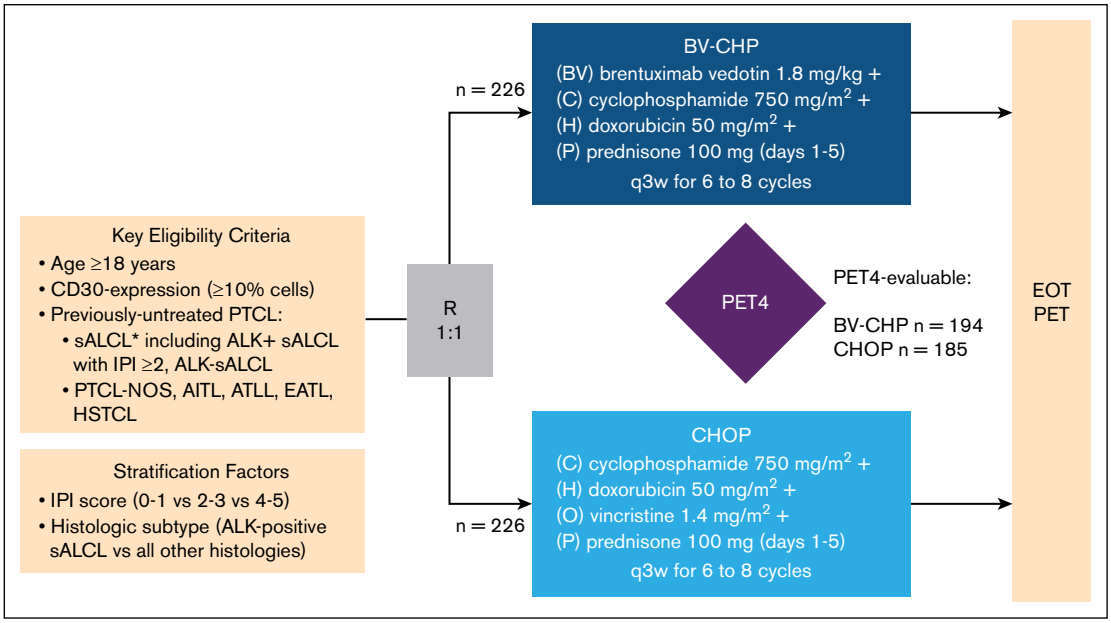

Figure 1. Study design of the ECHELON-2 trial. *Targeting 75% (±5%) ALCL per European Union and Canadian regulatory commitment. AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; IPI, International Prognostic Index; PTCL-NOS, PTCL, not otherwise specified; q3w, every 3 weeks; R, randomized.

defined as Deauville score of 1 to 3.[21] Complete response (CR) rate was defined as the proportion of patients with CR at the EOT.

Statistical analysis

PFS and OS by PET4 status in the overall population and in the sALCL subgroup were estimated by Kaplan-Meier methods; *P* values were based on stratified log-rank tests. All analyses were exploratory, and *P* values were descriptive.

Results

A total of 452 patients were randomly assigned to receive either BV-CHP (n = 226) or CHOP (n = 226). Median follow-up was 66.8 months (range, 0-90 months), which was longer than the 47.6-month follow-up reported by Horwitz et al.[13] Baseline patient demographics and disease characteristics were balanced between treatment arms as previously described.[7] The median age was 58 years in both treatment arms (range, 18-85 years [BV-CHP arm] and 18-83 years [CHOP arm]). More patients were male in both the BV-CHP (59%) and CHOP (67%) arms. Most patients were either White (62% in the BV-CHP arm and 63% in the CHOP arm) or Asian (20% in the BV-CHP arm and 24% in the CHOP arm). Most patients enrolled had advanced disease (stage III, 27%; stage IV, 53%), and most patients (n = 316 [70%]) had sALCL, as per study design (supplemental Table 1). Eastern Cooperative Oncology Group performance status was 0, 1, and 2 in 37%, 40%, and 23% of patients in the BV-CHP arm, and 41%, 38%, and 21% of patients in the CHOP arm, respectively.

Of the overall population of 226 patients in each treatment arm, 32 patients in the BV-CHP arm and 41 in the CHOP arm were not evaluable for PET4. In the BV-CHP arm, 19 patients did not have PET4 due to discontinuing treatment before receiving 4 cycles. For the additional 13 patients who received ≥4 cycles, the reason is unknown. In the CHOP arm, 24 patients did not have PET4 due to discontinuing treatment before receiving 4 cycles. For the additional 17 patients who received ≥4 cycles, the reason is unknown. In the BV-CHP arm, 38% of patients completed treatment, 34% discontinued treatment due to adverse events, 9% discontinued due to investigator decision, 6% discontinued due to progressive disease, and 3% discontinued due to patient decision. In the CHOP arm, 29% of patients completed treatment, 32% discontinued treatment due to adverse events, 29% discontinued due to progressive disease, 2% discontinued due to investigator decision, 2% discontinued due to patient decision, and 5% discontinued due to other reasons. In the sALCL subgroup, of the 162 patients in the BV-CHP arm, 19 were not evaluable and of the 154 patients in the CHOP arm, 32 were not evaluable for PET4.

Outcomes by PET4 status

In the overall population, 194 patients in the BV-CHP arm and 185 in the CHOP arm were PET4 evaluable. Of these patients, 93% completed treatment, 3% discontinued treatment due to progressive disease, 2% discontinued due to adverse events, 2% discontinued due to patient decision, and 1% discontinued due to investigator decision in the BV-CHP arm. In the CHOP arm, 90% completed treatment, 8% discontinued treatment due to progressive disease, 1% discontinued due to adverse events, 1% discontinued due to patient decision, and 1% discontinued due to investigator decision. In the sALCL subgroup, 143 patients in the BV-CHP arm and 122 in the CHOP arm were PET4 evaluable. Of the PET4-evaluable patients in the overall population, 175 of 194 (90%) in the BV-CHP arm and 147 of 185 (79%) in the CHOP arm had a PET4-negative scan, whereas 19 of 194 (10%) in the BV-CHP arm and 38 of 185 (21%) in the CHOP arm had a PET4-positive scan. Of the PET4-evaluable patients in the sALCL subgroup, 128 of 143 (90%) in the BV-CHP arm and 98 of 122

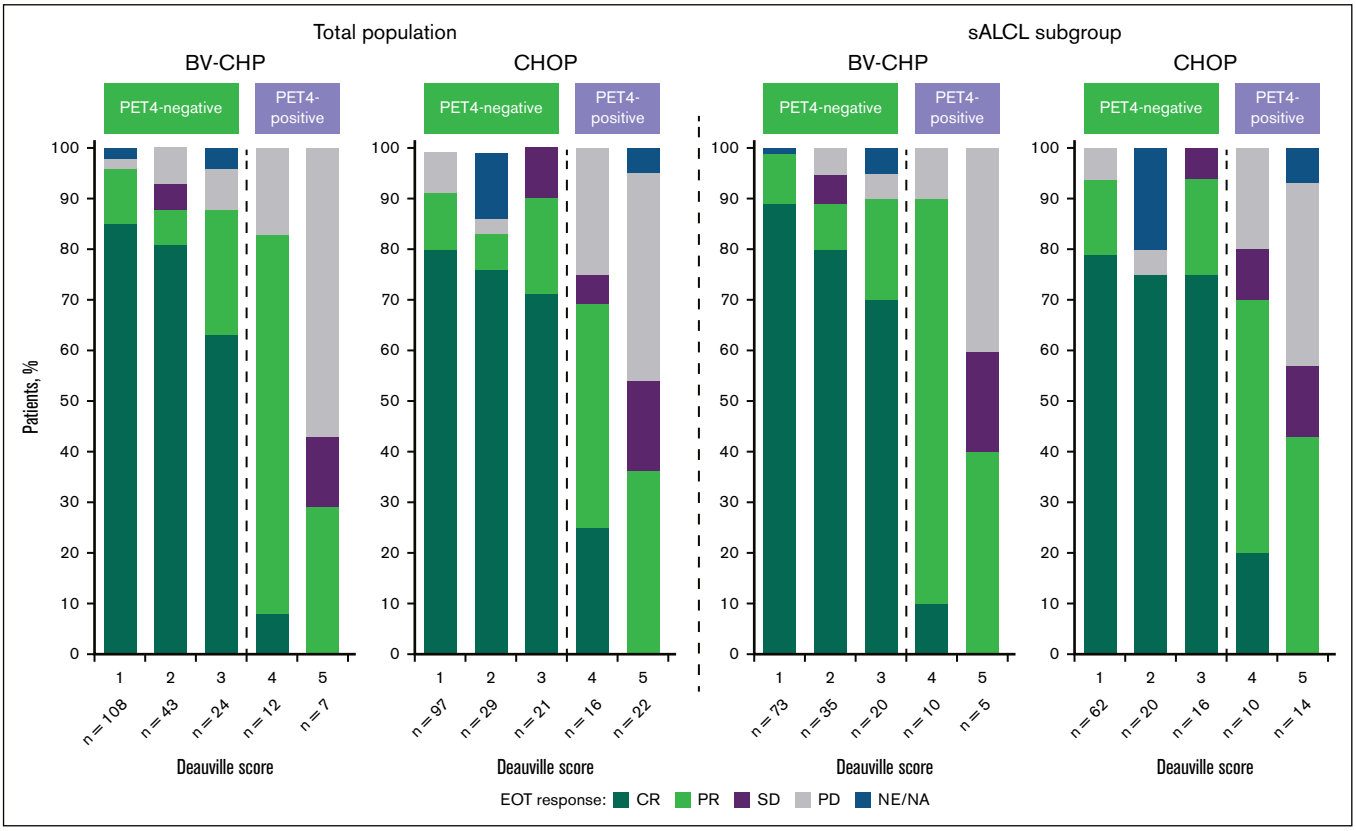

Figure 2. Cycle 4 PET status and EOT response in the total population and sALCL subgroup. NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

(80%) in the CHOP arm were PET4 negative. Among the overall population of PET4-evaluable patients in the BV-CHP arm, not surprisingly, the PET4-negative subgroup (Deauville score 1-3) had a higher CR rate (142/175 [81%]) than the PET4-positive subgroup (Deauville score 4-5; 1/19 [5%]) at EOT (Figure 2). Among the PET4-evaluable patients in the CHOP arm, the PET4-negative subgroup also had a higher EOT CR rate (115/147 [78%]) than the PET4-positive subgroup (4/38 [11%]; Figure 2). The EOT CR rates were similar in the PET4-negative subgroups in the BV-CHP (81%) and CHOP (78%) arms.

The PET4-negative patients in both treatment arms had improved PFS compared with those with a PET4-positive scan in both the overall population (Figure 3A-B) and the sALCL subgroup (Figure 4A-B). In the BV-CHP arm of the overall population, median PFS was not reached for PET4-negative patients and was 9.0 months for PET4-positive patients (HR, 0.36; 95% CI, 0.19-0.66; $P = .0006$); 3-year PFS rates were 67% and 40%, respectively. In the BV-CHP arm of the sALCL subgroup, median PFS was also not reached for PET4-negative patients and was 12.7 months for PET4-positive patients (HR, 0.28; 95% CI, 0.14-0.60; $P = .0004$); 3-year PFS rates were 76% and 44%, respectively. In the CHOP arm of the overall population, median PFS was 63.8 months for PET4-negative patients and 5.4 months for PET4-positive patients (HR, 0.26; 95% CI, 0.17-0.41; $P < .0001$); 3-year PFS rates were 61% and 22%, respectively. In the CHOP arm of the sALCL subgroup, median PFS was 64.7 months for PET4-negative patients and 5.8 months for PET4-positive patients (HR, 0.31; 95% CI, 0.17-0.56; $P < .0001$); 3-year PFS rates were 68% and 30%, respectively.

The PFS analyses per Deauville score 1 through 5 are shown in supplemental Figures 1A-B and 2A-B, and highlight the very poor outcome of those with PET4 Deauville score 5, regardless of treatment arm. In the BV-CHP arm of the overall population (supplemental Figure 1A), median PFS was not reached in patients with Deauville score 1, not reached in those with Deauville score 2, not reached in those with Deauville score 3, 48.2 months in those with Deauville score 4, and 3.9 months in those with Deauville score 5; 3-year PFS rates were 66%, 65%, 75%, 55%, and not estimable, respectively. In the CHOP arm of the overall population (supplemental Figure 1B), median PFS was 63.8 months in patients with Deauville score 1, 30.8 months in those with Deauville score 2, not reached in those with Deauville score 3, 7.6 months in those with Deauville score 4, and 4.4 months in those with Deauville score 5; 3-year PFS rates were 62%, 50%, 71%, 27%, and 18%, respectively.

In the BV-CHP arm of the sALCL subgroup (supplemental Figure 2A), median PFS was not reached in patients with Deauville score 1, not reached in those with Deauville score 2, not reached in those with Deauville score 3, 48.20 months in those with Deauville score 4, and 3.94 months in those with Deauville

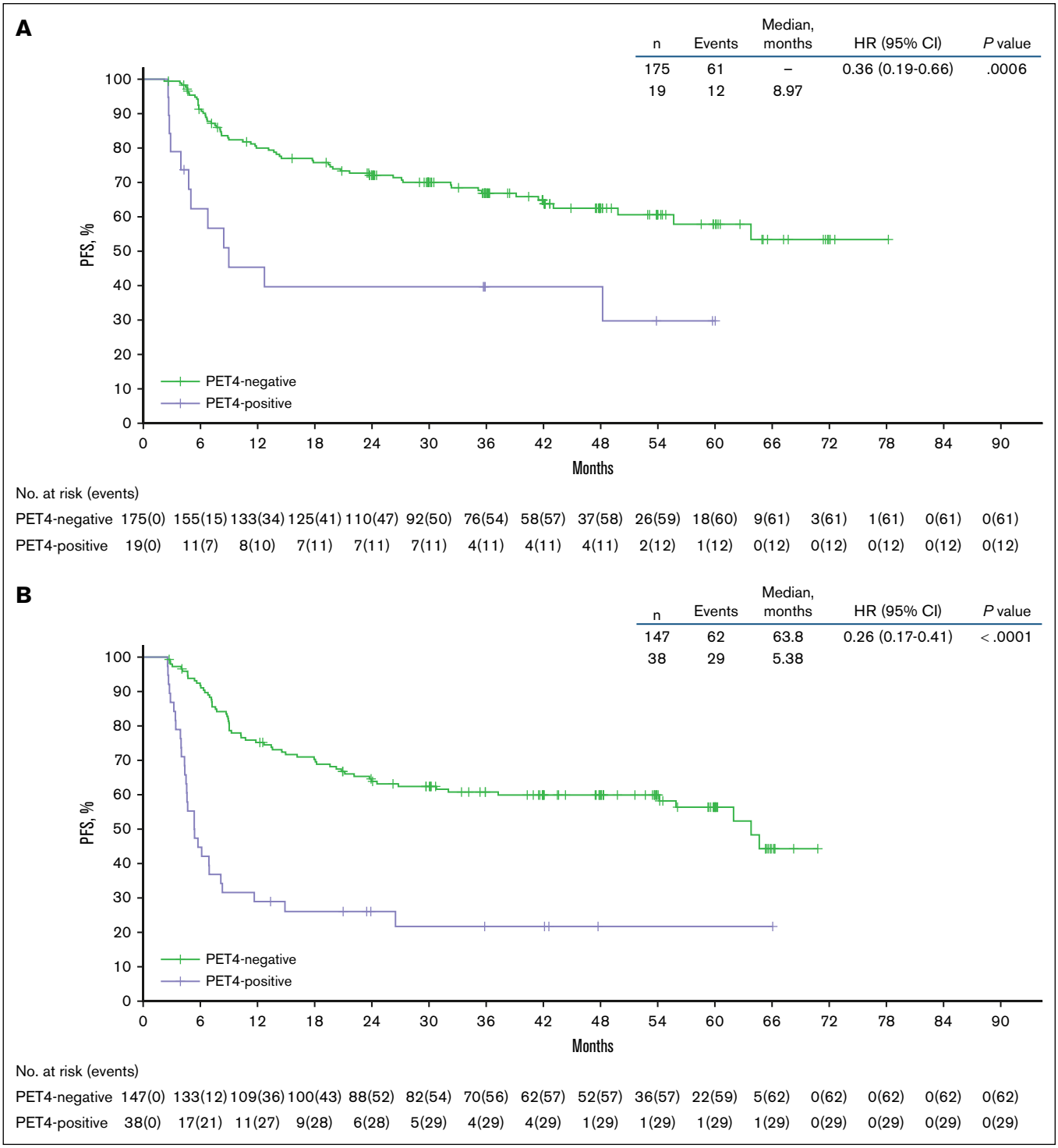

Figure 3. Kaplan-Meier estimate of PFS and OS by cycle 4 PET status in the total population. PFS in the BV-CHP (A) and CHOP (B) arms, and OS in the BV-CHP (C) and CHOP (D) arms.

score 5; 3-year PFS rates were 76%, 70%, 85%, 56%, and not estimable, respectively. In the CHOP arm of the sALCL subgroup (supplemental Figure 2B), median PFS was 64.66 months in patients with Deauville score 1, not reached in those with Deauville score 2, not reached in those with Deauville score 3, 14.88 months in those with Deauville score 4, and 4.97 months in those with Deauville score 5; 3-year PFS rates were 69%, 59%, 75%, 32%, and 29%, respectively.

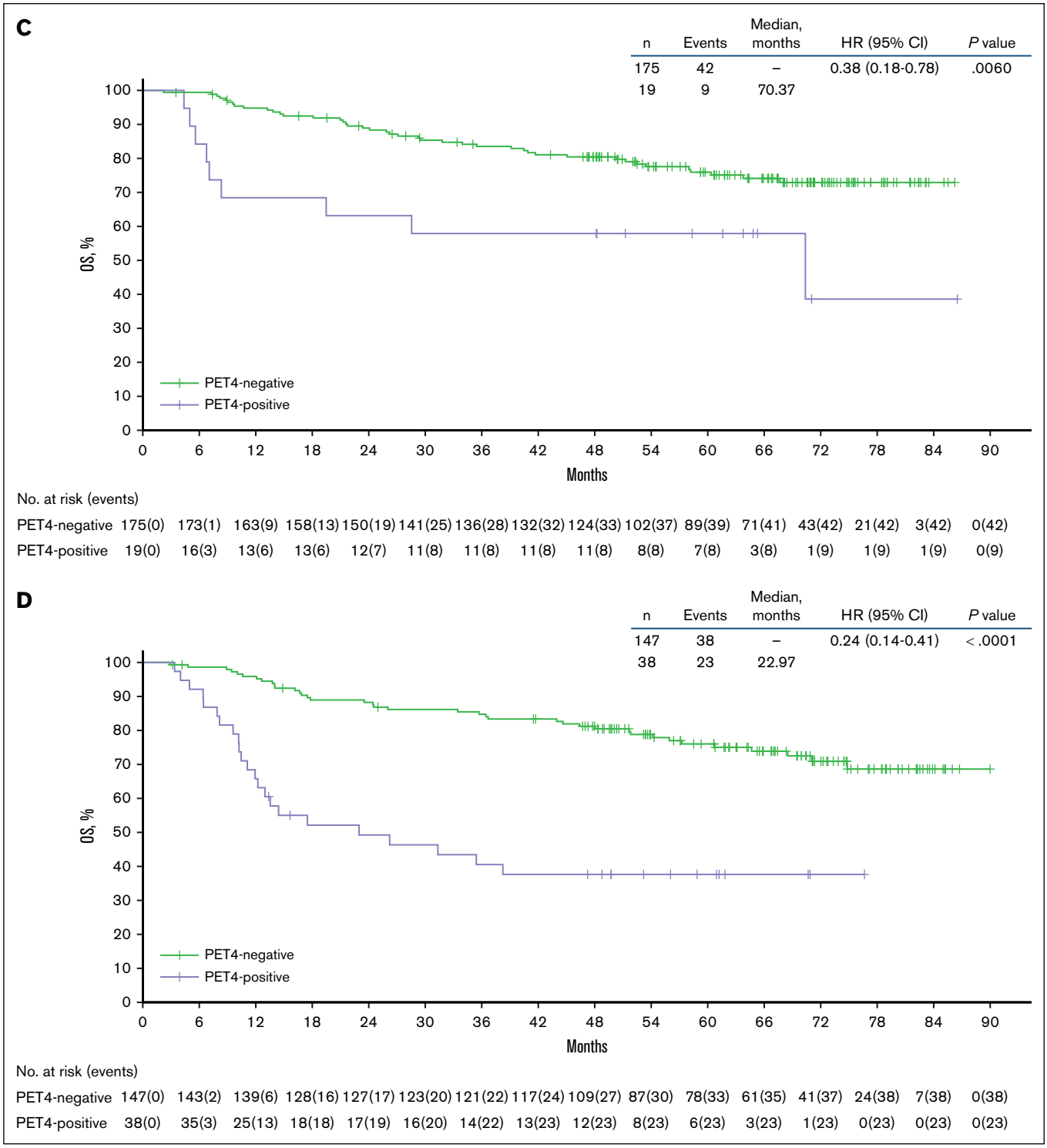

Figure 3 (continued)

A sensitivity analysis of PFS was conducted in which receipt of new anticancer therapy was not considered an event or a reason for censoring, and in which patients who died or progressed after >1 consecutively missed radiographic tumor assessment were considered to have had an event on the date of death or progression. Median PFS was 63.8 months for PET4-negative patients and 12.7 months for PET4-positive patients in the BV-CHP arm (supplemental Figure 3A). In the CHOP arm, median PFS was 63.8 months for PET4-negative patients and 6.3 months for PET4-positive patients (supplemental Figure 3B).

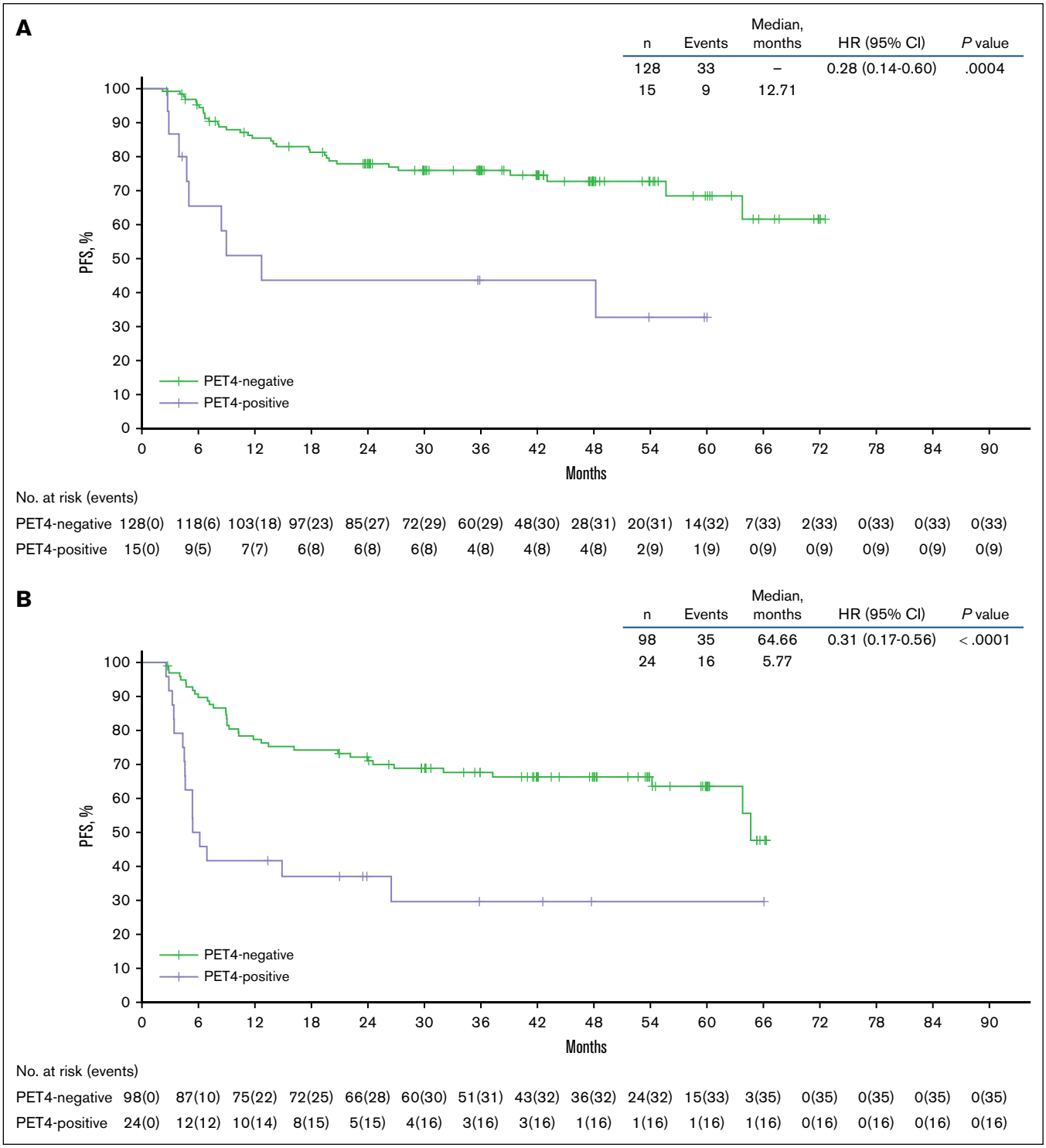

Figure 4. Kaplan-Meier estimate of PFS and OS by cycle 4 PET status in the sALCL subgroup. PFS in the BV-CHP (A) and CHOP (B) arms, and OS in the BV-CHP (C) and CHOP (D) arms.

The PET4-negative patients in both treatment arms had improved OS compared with those who were PET4 positive, in both the overall population (Figure 3C-D) and the sALCL subgroup (Figure 4C-D). In the BV-CHP arm, median OS was not reached in the overall population for PET4-negative patients and was 70.4 months for PET4-positive patients (HR, 0.38; 95% CI, 0.18-0.78; $P = .0060$). Similarly, in the sALCL subgroup, median OS was not reached for PET4-negative patients and was 70.4 months for PET4-positive patients (HR, 0.38; 95% CI, 0.16-0.94; $P = .0292$). In the CHOP arm, median OS was not reached in the overall

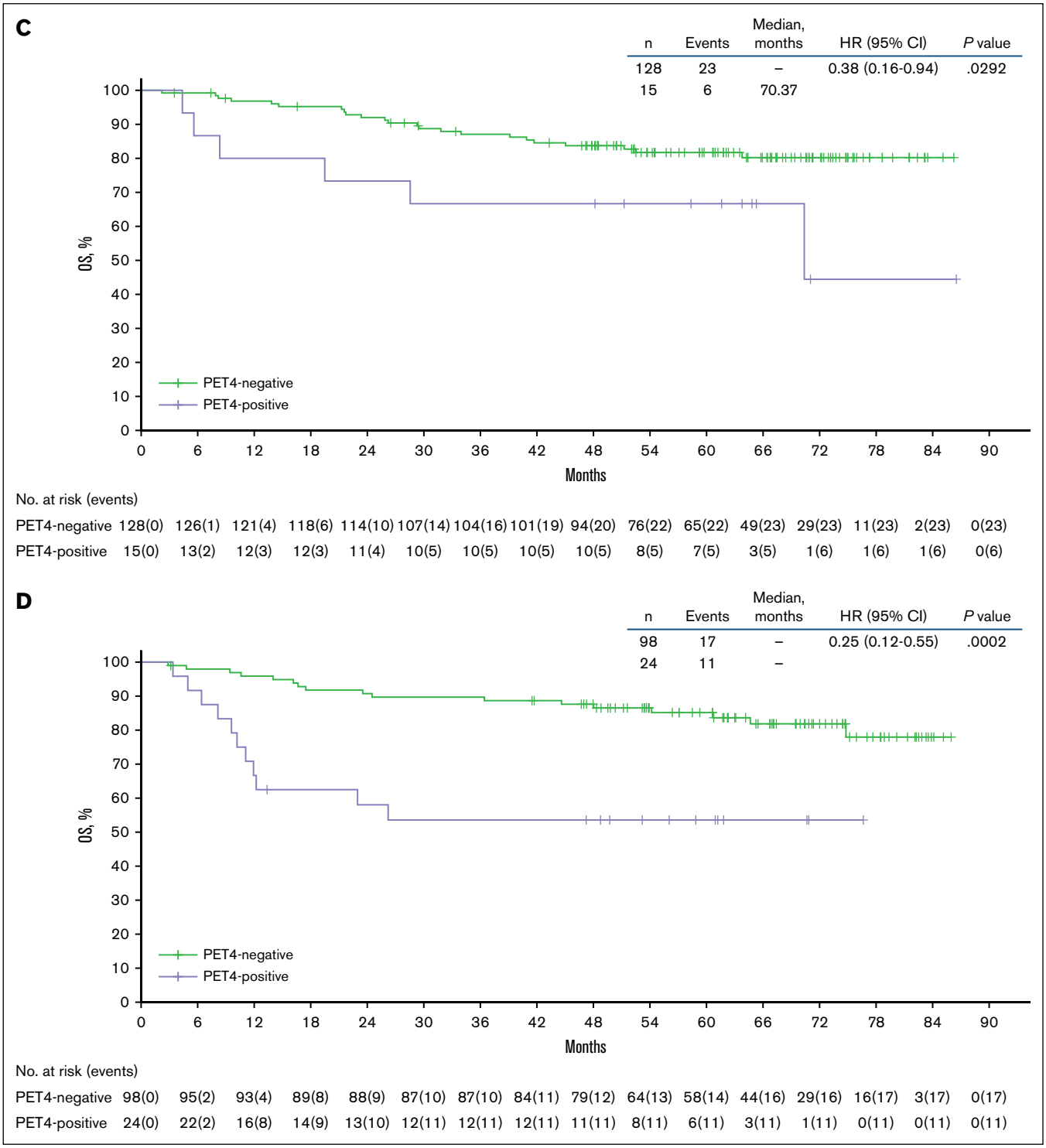

Figure 4 (continued)

population for PET4-negative patients and was 23.0 months for PET4-positive patients (HR, 0.24; 95% CI, 0.14-0.41; $P < .0001$). Median OS in the sALCL subgroup was also not reached for PET4-negative or -positive patients (HR, 0.25; 95% CI, 0.12-0.55; $P = .0002$). The OS analyses per Deauville score 1 through 5 are shown in supplemental Figures 1C-D and 2C-D. In the BV-CHP arm, median OS was not reached in patients with Deauville score 1 to 4 and was 8.3 months in those with Deauville score 5. In the CHOP arm, median OS was not reached in patients with Deauville score 1 to 4 and was 12.1 months in those with Deauville score 5.

Discussion

PET4-negative status, as determined by Deauville score 1 to 3, was associated with improved long-term PFS and OS in both the BV-CHP and CHOP arms compared with those with PET4-positive status. Compared to patients in the CHOP arm, PFS was qualitatively better in the BV-CHP arm. The results in the sALCL subgroup were consistent with those of the overall PET4-evaluable population of patients with $CD30^+$ PTCL. In this subgroup, median OS was not reached in both PET4-negative and PET4-positive patients in the CHOP arm, likely due to these patients transitioning to alternative therapies, including BV. As reported previously, more patients in the CHOP arm received subsequent BV.[13] As most evaluable patients with PET4-positive status in the total population did not reach CR at EOT, PET4-positive status was found to be predictive of lack of CR achievement, highlighting that use of interim PET after 4 cycles may facilitate the selection of patients for alternate therapies. Although patient numbers were small, this was particularly evident for those with Deauville score 5 following PET4, as this was also associated with very poor PFS and OS (median PFS, 3.9 months with BV-CHP and 4.4 months with CHOP; median OS, 8.3 months with BV-CHP and 12.1 months with CHOP; supplemental Figure 1A-D). Patients with Deauville score 5 after PET4-positive scans may be early candidates for clinical trials, without having to wait for disease progression. Results of the sensitivity analysis evaluating the impact of new anticancer therapy on PFS were consistent with the main analysis.

The prognostic value of interim PET in PTCL has been evaluated in several retrospective studies. A retrospective study of 140 patients from 7 European centers assessed the value of interim PET after 3 or 4 cycles of a first-line anthracycline-based chemotherapy and found that interim PET response was predictive of outcomes and may allow for patients with high-risk PTCL to be detected earlier. Two-year PFS and 2-year OS for patients with PET3/4-positive (Deauville score ≥ 4; $n = 28$) were 16% and 32%, respectively; for PET3/4-negative scans (Deauville score <4; $n = 67$),[9] 2-year PFS and 2-year OS were 75% and 85%, respectively.[9]

A prospective cohort study in Korea analyzed the prognostic value of a PET2 or PET3 scan in patients with newly diagnosed PTCL treated with CHOP every 21 days for 6 planned cycles. Three-year event-free survival (EFS) and OS for patients with interim PET-positive (Deauville score 4-5) scans were significantly shorter than those for patients with interim PET-negative scans (Deauville score 1-3; 3-year EFS, 29.4% vs 51.1%; 3-year OS, 55.3% vs 78.9%).[22]

In a retrospective study of patients with PTCL treated with CHOP or CHOP-like regimens with the intent to consolidate with ASCT, investigators re-evaluated baseline and interim PET4 images to assess the prognostic value of the Deauville score. In univariate analysis, a Deauville score of 4 or 5 at interim PET4 was found to be associated with worse EFS (HR, 3.6; 95% CI, 1.82-7.00; $P < .001$) and OS (HR, 11.0; 95% CI, 4.41-27.57; $P < .001$).[14]

Different interim PET intervals have been evaluated across several studies, and the optimal timing is unknown. In a retrospective single-center analysis of newly diagnosed patients with PTCL ($n = 49$), median PFS for Deauville scores of 1 through 3, 4, and 5 were 28, 10, and 2 months, respectively. Interim PET/CT after 4 cycles discriminated between PFS outcomes more clearly compared with interim PET/CT after 3 cycles,[23] while in a meta-analysis of 1692 patients with de novo diffuse large B-cell lymphoma treated with rituximab plus CHOP, interim PET after 4 cycles also predicted good response.[24] Current guidelines for patients with PTCL recommend interim restaging with CT or PET/CT (preferred) after 3 or 4 cycles of chemotherapy.[25]

In this analysis, interim PET was performed at cycle 4, which is consistent with guideline recommendations for PTCL. These results establish the role of interim PET in predicting long-term response and support further research in this area. Of interest, this varies from the ECHELON-1 trial that evaluated BV in combination with chemotherapy in patients with classic Hodgkin lymphoma, in which interim PET was evaluated at PET2 as per the recommended timing of interim PET in Hodgkin lymphoma.[12,26] In that study, results of PET at cycle 2 allowed for an optional switch to alternative treatment at the treating physician's discretion for patients with a Deauville score of 5.[27] The recently published phase 3 HD21 trial de-escalated treatment in patients who were PET2-negative to 4 rather than 6 cycles of BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone).[28] Ongoing trials, such as the AHOD2131 (NCT05675410) trial, are using PET2 for treatment decisions in Hodgkin lymphoma.

The Lugano criteria, also known as the revised response criteria, assess treatment response in FDG-avid lymphoma histologies using PET/CT scans according to the Deauville 5-point scale.[21,25] The more granular Deauville scale was used in this post hoc analysis of the ECHELON-2 trial to assess treatment response, rather than the Revised Response Criteria for Malignant Lymphoma[19] that was used in the primary analyses.[7,13] Previously in clinical trials, there had been differences in whether a score of 3 was considered to be PET-negative, especially for an interim scan; however, it is now widely considered that a score of 1 to 3 comprises PET-negative.[25] A PET-positive scan can be a Deauville score of 4 or 5, with the latter having a poor outcome, with the majority of patients ultimately progressing. In this analysis, patients with Deauville score of 4 showed better outcomes than those with Deauville score of 5 in both treatment arms. Response biomarkers like an interim PET scan have additional potential benefits, including minimizing further exposure to drugs that are not beneficial and preservation of performance status, which would facilitate administration of subsequent alternative lines of therapy.[29]

Our study was not able to evaluate the total metabolic tumor volume derived from baseline PET imaging. However, as a baseline biomarker, total metabolic tumor volume has also been proposed as a potential prognostic indicator in lymphoma before first-line treatment.[30] Baseline metabolic tumor volume may complement other clinical scores and molecular predictors to improve the stratification of patients into risk groups.[30] Circulating tumor DNA has also been used as a noninvasive tumor-specific biomarker for prognosis prediction in diffuse large B-cell lymphoma,[31] and initial results suggest the clinical relevance of plasma circulating tumor DNA in PTCLs.[32] The use of a composite end point combining metabolic tumor volume with other prognostic indicators to risk-adapt treatment has been evaluated retrospectively in patients with PTCLs[33,34]; however, further prospective research is needed.

These findings emphasize the potential of interim PET scans to support risk stratification and individualize therapy decisions, which may lead to improvement in patient outcomes in the management of patients with PTCLs. One limitation of this analysis is that this exploratory subgroup analysis was post hoc, which may introduce unknown bias and can limit definitive conclusions. Analysis of outcome differences between other PTCL subtypes was not done as the patient numbers in this analysis are too small to show meaningful differences. The study enrolled a high number of sALCL patients to comply with the regulatory guidance and therefore most patients (70%) had sALCL[13], leading to a lack of study population heterogeneity that can potentially limit the broad applicability of these results. In addition, PET4 was not evaluable in some patients due to treatment discontinuation before 4 cycles, most probably due to poor outcomes in these patients. Notably, a similar proportion of patients across both arms were not evaluable for PET4. In addition, OS results are potentially impacted by ASCT and subsequent anticancer therapy. In the ECHELON-2 trial, 22% of patients in the BV-CHP and 17% in the CHOP arms received ASCT, and 31% and 45%, respectively, received subsequent anticancer therapy.[13] Future prospective studies evaluating PET4 response as a prespecified end point are needed, as this study reiterates the important prognostic value of PET in patients with PTCL, both as interim and EOT evaluations.

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Authorship

Contribution: S.I., N.M.-S., and M.F. conceptualized the research; S.I., N.M.-S., K.F., and M.F. developed the methodology; K.F. provided curation, analysis, and verification of the study data; S.I., N.M.-S., R.A., N.B., J.C., F.M., E.D.-D., G.R., W.K., O.A., T.F., V.C., G.G., P.Z., D.B., J.M., I.C., J.C., K.S., and S.H. conducted the research; S.I. and M.F. prepared the original manuscript draft; S.I., N.M.-S., and M.F. provided overall study oversight; and all authors reviewed and edited the manuscript.

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