RESEARCH LETTER

blood advances

TO THE EDITOR:

Frontline chemoimmunotherapy with nivolumab and dose-adjusted EPOCH in peripheral T-cell lymphoma: a phase 1 trial

Bradley Haverkos,[1] Jasmine Zain,[2] Manali Kamdar,[1] Alexander Neuwelt,[3] Eduardo Davila,[4] Xander Bradeen,[1] Ajay Major,[1] Steven Bair,[1] Jagar Jasem,[1] Clayton Smith,[1] Diana Abbott,[1] and Pierluigi Porcu[5]

[1]Division of Hematology, University of Colorado, Aurora, CO; [2]Division of Hematology, City of Hope, Duarte, CA; [3]Division of Hematology and Oncology, Virginia Commonwealth University, Richmond, VA; [4]Division of Oncology, University of Colorado, Aurora, CO; and [5]Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation, Department of Medical Oncology, Thomas Jefferson University Hospital, Philadelphia, PA

Except for anaplastic–large cell lymphoma, 5-year progression free survival (PFS) for peripheral T-cell lymphomas (PTCLs) with anthracycline-based chemotherapy is ~25%.[1,2] Dose adjusted (DA)-EPOCH (etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide) is an anthracycline-based regimen for PTCLs.[3-6] The programmed death (PD) pathway is an inhibitory immune checkpoint that downregulates T-cell activation and proliferation. PD-1 or PD-L1 expression on neoplastic T cells and stromal or innate immune cells is common in T-cell neoplasms.[7,8] Checkpoint blockade (CPB) with anti-PD1 monoclonal antibodies produced an overall response rate (ORR) of ~30% in pretreated PTCLs.[9-11] Cytotoxic chemotherapy has additive efficacy when combined with CPB[12-17]; however, the immune-enhancing effect of CPB in untreated patients with PTCL may lead to excessive toxicity or hyper-progression.[18,19] To assess the safety and preliminary efficacy of frontline CPB+chemotherapy in PTCLs, we conducted a phase 1 trial of nivolumab (Nivo) in combination with DA-EPOCH.

This was a multicenter, single arm, phase 1 trial of fixed dose Nivo combined with standard DA-EPOCH[20] in PTCLs. Because patients were treated with curative intent, we designed stopping rules for both toxicity and efficacy. The study was to be halted if ≥2 treatment-related deaths occurred, or 3 out of the first 10 patients experienced severe immune-related adverse events (irAEs). The sample size was designed to provide >80% power (with a type 1 error rate of 0.1) that the true probability of achieving a complete response (CR) did not fall <30%. Although 17 patients were needed to achieve 80% power, 18 total patients were enrolled in the study to account for possible dropout or loss to followup. Key eligibility criteria included absolute neutrophil count >1000 cells/mm^3 unless due to lymphoma, platelet count >100 000/μL, or >50 000/μL if bone marrow involvement or splenomegaly, and adequate organ function. Patients were excluded if they received immunosuppressive therapy (besides medications used to treat lymphoma) within 7 days of study treatment or had an autoimmune condition requiring immunosuppressive therapy within the prior 2 years.

The planned duration of therapy was 6 cycles of chemotherapy (6 cycles of Nivo + DA-EPOCH or 5 cycles of Nivo + DA-EPOCH if patient received a cycle of anthracycline-based chemotherapy before enrollment). Nivolumab (360 mg) was administered on day 1 followed by DA-EPOCH, with 21-day cycles. DA-EPOCH was dose adjusted according to CALGB 50303,[20] with the exception that rituximab was not administered, and patients could begin the first cycle of treatment at dose level −1 (ie, 600 mg/m^2 cyclophosphamide) at investigator discretion. For serious irAEs, systemic glucocorticoids were administered per institutional guidelines. For any irAE, Nivo was held until resolution to grade 1 and on ≤10 mg prednisone. For any grade 3 irAE suspected to be attributable to Nivo, Nivo was withheld during the subsequent cycle. If the same grade 3 irAE recurred, Nivo was permanently discontinued. For severe grade 3 irAEs (ie, pneumonitis, myocarditis, and infusion reactions) or grade 4 irAEs, Nivo was omitted for all remaining DA-EPOCH cycles. Patients had the option to proceed to autologous stem cell transplant (ASCT) or surveillance, according to patient and physician preference.

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CTCAE v5.0 was used to grade all AEs. Responses were assessed using positron emission tomography-computed tomography after 2 cycles of Nivo + DA-EPOCH and after the last cycle, using RECIL criteria.[21]

Baseline characteristics are summarized in Table 1. Nine of the 18 (50%) patients received treatment before enrollment for urgent cytoreduction or symptom control, consisting of a cycle of anthracycline-based combination chemotherapy (N = 6, 33%), steroids (N = 2, 11%), and oral methotrexate (N = 1, 6%, SPTCL). The median DA-EPOCH dose level across all cycles was −1 (range: −6 to +3). All dose level reductions were due to grade 4 thrombocytopenia, and none for neutropenia. In total, 8 of 77 cycles (10%) were delayed >3 days. Reasons for delay were suspected pneumonitis (N = 1), infections (N = 4), grade 3 neuropathy (N = 1), grade 3 abdominal pain (N = 1), and neutropenic fever (N = 1). Sixteen of 18 patients (88.8%) completed all planned cycles. Two patients discontinued treatment after cycle 4 because of inadequate response. Two patients proceeded to ASCT.

Table 1. Baseline characteristics of 18 patients treated with Nivo + EPOCH

Baseline characteristics	N = 18 (%)
Subtype	
Peripheral T-cell lymphoma NOS	7 (38.9%)
T-cell lymphomas with a FH phenotype	6 (33%)
Primary cutaneous γ/δ T-cell lymphoma	2 (11.1%)
Anaplastic large cell lymphoma, ALK-	2 (11.1%)
Subcutaneous panniculitis like T-cell lymphoma	1 (5.6%)
CD30 expression >10%*	2 (11%)
EBV-associated†	6 (33%)
Age	
Median	66
Range	43-77
Sex, M	10 (58.8%)
ECOG PS	
0-1	7 (38.9%)
2	11 (61.1%)
Stage	
III	1 (5.6%);
IV	17 (94.4%)
LDH, greater than normal	10 (55.6%)
Extranodal sites, 2 or more	7 (41.2%)
IPI	
Low (0-1)	3 (17%)
Intermediate (2-3)	6 (33%)
High (4-5)	9 (50%)

FH, follicular helper; NOS, not otherwise specified; M, male; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, international prognostic indices; among the peripheral T-cell lymphomas with a follicular helper phenotype, 4 were angioimmunoblastic T-cell lymphomas and 2 were FH TCL NOS. The subcutaneous panniculitis like T-cell lymphoma did not respond to methotrexate before enrollment.

*Only the 2 ALCLs had >10% expression.

†Epstein-Barr virus association or positivity was defined as any EBER positivity or elevated viral load measured using polymerase chain reaction.

All 18 patients experienced ≥1 grade 1 to 2 and 10 (56%) experienced grade 3 to 4 nonhematologic toxicities from EPOCH. The most common nonhematologic grade 2 to 4 AEs were febrile neutropenia, neuropathy, and gastrointestinal events. irAEs of all grades occurred in 78% (N = 14) of patients and 39% (N = 7) experienced ≥grade 3 irAEs. Forty-four percent (N = 8) of patients had a serious irAE leading to a Nivo dose hold or discontinuation, all of which occurred before cycle 4 (6 of 8 events occurred before cycle 3). Events included rash/Stevens-Johnson syndrome (N = 1), pneumonitis (N = 2), colitis (N = 1), encephalitis (N = 1), immune-mediated thrombocytopenia (N = 1), hemolytic anemia (N = 1), and fever (N = 1). Other irAEs (not dose limiting) were observed during later cycles, including transaminitis, pruritus, thyroiditis, and vitiligo. Of the 8 patients who had a protocol defined dose hold or discontinuation of Nivo, 2 resumed Nivo after a single dose/cycle hold, and the other 6 discontinued Nivo for remaining cycles. We compared frequency of irAEs among individuals whose first cycle of chemotherapy was Nivo + DA-EPOCH (N = 12) vs those who received a cycle of anthracycline-based chemotherapy before enrollment on trial (N = 6). All of the serious irAEs resulting in dose hold or discontinuation of Nivo occurred in the 12 patients whose first cycle was Nivo + DA-EPOCH; none occurred in the 6 who received 1 prior cycle.

Interim responses were CR (N = 6), partial response (PR) (N = 11), and stable disease (SD) (N = 1) for an interim overall response rate (ORR) of 94%. End-of-treatment (EOT) responses were CR (N = 11), PR (N = 5), and progressive disease (N = 2) for an EOT ORR of 89% (CR 61%). Figure 1 shows EOT response and subsequent outcomes. With a median follow up of >2.5 years (32.1 months; 95% confidence interval [CI], 13.3-44.9), median EFS (events defined as start of new treatment, progression, or death) was 10.5 months (95% CI, 6.9-20.5), median PFS was 14.5 months (95% CI, 7.5-22.2), and median overall survival was 23.8 months (95% CI, 10.3-not reached). In a χ^2 analysis, patients who received more doses of Nivo were more likely to achieve CR ($P = .0066$) and had significantly better EFS ($P = .0068$).

The primary goal of this study was to assess the feasibility of combined CPB and chemotherapy as first-line therapy in PTCL and determine the frequency and severity of irAEs. Overall, 78% of patients experienced an irAE, similar to that observed in the pivotal phase 1 CPB study in relapsed classical Hodgkin lymphoma (cHL).[22] However, we observed more frequent early and severe dose-limiting irAEs, with 88% of the serious irAEs occurring after 1 or 2 doses of Nivo, as compared with the phase 1 study in cHL in which only 9% of patients had to discontinue CPB because of toxicity and all received >5 doses.[22] Patients who received a cycle of anthracycline-based chemotherapy before enrollment did not experience any dose limiting irAEs. Studies have suggested that cytotoxic chemotherapy may enhance antitumor T-cell responses when combined with CPB.[17,23-25] Although our sample is small, we observed statistically more CRs and longer EFS in patients who received more Nivo and patients with known chemorefractory subtypes, such as PCGDTCL, achieved durable responses. In conclusion, Nivo + DA-EPOCH had encouraging efficacy and safety when anthracycline-based chemotherapy was administered

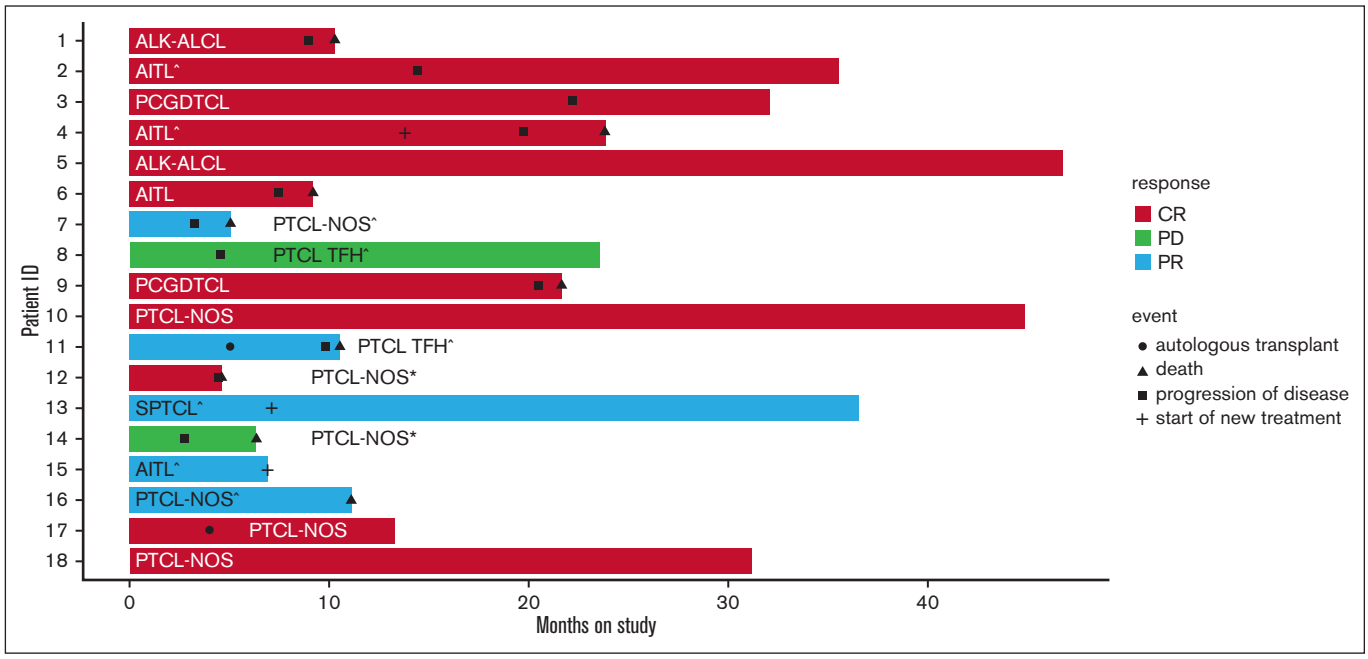

Figure 1. End-of-therapy response and corresponding survival. ^Patients 2, 4, 7, 8, 11, 13, 15, and 16 had to omit nivolumab for at least 1 cycle due to irAE. *Patients 12 and 14 expressed cytototoxic markers (ie, granzyme and/or TIA). Patients 2, 4, 6, 8, 11, and 17 were EBV-associated as defined in Table 1. PD, progressive disease.

before Nivo, without hyperprogression events. Further investigation of frontline chemoimmunotherapy in PTCL is warranted using a sequential approach.

The trial was approved by all Institutional Review Boards and registered at www.clinicaltrials.gov as #NCT03586999.

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Contribution: B.H., A.N., and P.P. designed the study; B.H., P.P., and D.A. analyzed and interpreted the data; P.P., B.H., and J.Z. acquired data for this study by enrolling patients; and all authors substantively revised the manuscript, approved the submitted version, and agreed to be both personally accountable for the author's own contributions and ensure that questions related to the accuracy or integrity of any of part of this work have been appropriately investigated and resolved.

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ORCID profiles: B.H., 0000-0002-3872-0615; J.Z., 0000-0003-4308-629X; E.D., 0000-0001-9738-4167; X.B., 0000-0002-5731-2860; P.P., 0000-0002-8056-023X.

Correspondence: Bradley Haverkos, Division of Hematology, University of Colorado, Anschutz Medical Campus, 1665 Aurora Ct, Aurora, CO 80045; email: Bradley.haverkos@CUAnschutz.edu.

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