Results from a phase I trial of pembrolizumab plus vorinostat in relapsed/refractory B-cell non-Hodgkin lymphoma

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Abstract

Outcomes after programmed death-1 (PD-1) blockade in B-cell lymphomas are disappointing with few durable responses. Histone deacetylase inhibitors exhibit favorable immunomodulatory effects and demonstrate synergistic anti-tumor immune responses with anti-PD-1 therapy in preclinical models. We, therefore, developed a phase I study to evaluate the safety and preliminary efficacy of pembrolizumab with vorinostat in relapsed/refractory B-cell lymphomas. Patients were treated in a dose-escalation cohort using a Rolling 6 design followed by an expansion cohort at the recommended phase II dose (R2PD). Fifty-two patients were enrolled (32 Hodgkin and 20 non-Hodgkin lymphoma [NHL]). Here, we report safety data from the dose escalation cohort, and the toxicity and efficacy within NHL patients. Vorinostat was administered twice daily on days 1-5 and 8-12 (dose-level [DL]1: 100 mg; DL2: 200 mg) and pembrolizumab (200 mg) was administered on day 1 of each 3-week cycle. Of six patients treated at DL1, one had a dose-limiting toxicity (DLT) (Stevens-Johnson syndrome [SJS]), and one of six had a DLT at DL2 (thromboembolism); therefore, DL2 was the RP2D. The patient developing SJS was treated with corticosteroids, infliximab, and cyclosporine but ultimately died of invasive fungal infection from the extensive immunosuppression used to treat the SJS. The most common adverse events were hypertension, diarrhea, and cytopenias. Of 20 NHL patients, nine had follicular lymphoma (FL) and 11 had diffuse large B-cell lymphoma (DLBCL). Five DLBCL patients had primary mediastinal B-cell lymphoma (PMBL). The complete and overall response rates (CR and ORR) were 11% and 22% for FL and 45% and 55% for all DLBCL. Amongst DLBCL, the CR and ORR was 80% and 80% for PMBL and 17% and 33% for non-PMBL. In conclusion, pembrolizumab with vorinostat was tolerable and produced responses in relapsed/refractory B-cell NHL, with particularly notable efficacy in PMBL (*clinicaltrials gov. Identifier: NCT03150329*).

Introduction

B-cell non-Hodgkin lymphoma (NHL) such as follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are the most common lymphomas diagnosed in the United States.[1] Currently, most FL and a large proportion of DLBCL patients will develop relapsed/refractory (r/r) disease, which has been historically associated with poor outcomes in the chemotherapy era.[2,3] More recently, however, the treatment paradigm of r/r DLBCL and FL has shifted away from conventional chemotherapy and towards the use of highly effective novel immunotherapies. This includes the recent development of CD19-directed chimeric antigen receptor (CAR) T cells,[4] CD20 bispecific antibodies (BsAb),[5] antibody drug conjugates (e.g., polatuzumab vedotin, loncastuximab tesirine),[6,7] and other antibody-based therapies (e.g., tafasitamab).[8] These treatments are each associated with high response rates and have greatly improved outcomes in patients with r/r B-cell NHL. However, despite these therapeutic advances, the reality remains that the majority of patients with r/r B-cell NHL will still not achieve a durable remission with immunotherapy or more traditional approaches like stem cell transplantation.[2,4,5] Treatment options are also limited for patients who progress after CAR T-cell therapy or stem cell transplantation, and the median overall survival (OS) is only 5.2 months for patients

with aggressive B-cell lymphomas relapsing after CAR T-cell therapy.[9] The development of safe and effective therapies for r/r B-cell NHL, therefore, remains an area of significant unmet need

The clinical efficacy of PD-1 blockade has transformed the treatment landscape of a number of cancer types.[10–13] The outcomes of anti-PD-1 monotherapy in r/r B-cell NHL, however, have been disappointing. For instance, the response rates to single-agent PD-1 blockade in r/r FL and DLBCL are only 4% and 10%, respectively.[14,15] The one notable exception are B-cell NHL that harbor programmed death-1 (*PD-L1*) gene alterations, including gray zone lymphomas, primary mediastinal B-cell lymphoma (PMBL), and certain subtypes of DLBCL.[16–18] In r/r PMBL for instance, up to 50% of patients respond to anti-PD-1 monotherapy. However, while complete responses (CR) appear durable, only a minority of PMBL patients achieve CR and the majority will eventually progress following anti-PD-1 therapy.[17] This presents a major challenge in a population of patients commonly defined by young age and where cure is the goal of treatment. Given these challenges, we sought to investigate whether a PD-1-based combination regimen could result in improved outcomes.

Histone deacetylase inhibitors (HDACi) such as vorinostat are epigenetic-modifying cancer treatments that are Food and Drug Administration-approved for the treatment of certain NHL.[19,20] HDACi also exhibit favorable immunomodulatory effects that improve anti-tumor immune responses generated in the setting of PD-1 blockade in various preclinical tumor models.[21–24] HDACi, for example, enhance tumor antigen presentation, increase recruitment of T cells into the tumor environment, and promote the function of tumor-reactive T cells, which results in significantly improved responses to PD-1 blockade therapy in preclinical models.[21–24] HDACi also increase PD-L1 expression on malignant cells from various tumor types, which may be an important determinant associated with PD-1 response in lymphoma and other malignancies.[23] HDACi and other epigenetic modifying therapies (DNMT3A inhibitors) have now been studied in combination with PD-1 blockade for a number of cancers and there have been early clinical signs of potential synergy.[21,25,26] In classic Hodgkin lymphoma (cHL), for example, the combination of PD-1 blockade with DNMT3Ai was associated with a higher CR rate and progression-free survival (PFS) compared to anti-PD-1 monotherapy.[25,26] We, therefore, hypothesized that adding the immunomodulatory pan-HDACi, vorinostat, to the anti-PD1 antibody, pembrolizumab, in patients with r/r FL, DLBCL, PMBL, and cHL would be safe and boost the anti-tumor activity of PD-1 blockade in B-cell lymphomas. Here we report the results of our phase I clinical trial evaluating the safety and preliminary efficacy of pembrolizumab with vorinostat in r/r B-cell lymphomas. In this manuscript, we report the safety data from the dose escalation cohort and the toxicity data and efficacy results from the NHL cohort of patients.

Methods

Patients

This was a single-center phase I dose-escalation trial with a planned expansion cohort. Eligible patients were 18 years old or older with r/r FL, DLBCL, PMBL, or cHL who had relapsed or progressed after at least one prior line of therapy and were transplant-ineligible or who refused transplant. Initially, prior anti-PD-1 exposure was allowed if patients had evidence of a prior objective response to PD-1 blockade. On May 14, 2019, the protocol was amended to allow patients to enroll regardless of response to prior anti-PD-1 therapy to facilitate study enrollment and assess efficacy in patients with cHL who progressed on prior PD-1 blockade. Additional inclusion criteria were as follows: Eastern Cooperative Oncology Group performance status of 0-1, total bilirubin ≤1.5x upper limit of normal (ULN) or direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5x ULN, AST/ALT ≤2.5x ULN, and PT/INR ≤1.5x ULN and PTT (aPTT) ≤1.5x ULN unless the patient was receiving anticoagulant therapy in which case PT or PTT had to be within therapeutic range of the intended use of anticoagulants. Patients with known Gilbert's disease were allowed to have a total bilirubin of up to ≤3x ULN and AST/ALT up to ≤3x ULN, and patients with lymphomatous involvement of the liver were allowed to be enrolled as long as AST/ALT ≤5x ULN. Hematologic parameters required were as follows: absolute neutrophil count (ANC) ≥1,000/μL, platelet count (Plt) ≥75,000/μL, and hemoglobin ≥8 g/dL without use of an erythropoiesis-stimulating agent within 7 days of assessment; patients with known bone marrow involvement by lymphoma were not required to meet these parameters. Patients had to be willing to provide tissue from a fresh core or excisional biopsy prior to starting study therapy or from archival tissue of a biopsy that was performed after the most recent systemic therapy. Other exclusion criteria included a diagnosis of immunodeficiency or any immunosuppressive therapy including systemic corticosteroids within 7 days prior to the first dose of trial treatment, prior allogeneic stem cell transplantation within 5 years or active graft-*versus*-host-disease, prior autoHCT within 60 days, active autoimmune disease requiring systemic treatment (replacement therapy such as thyroxine or insulin excepted), history of non-infectious pneumonitis requiring steroids or current pneumonitis, or a QT interval corrected for heart rate (QTc) >470 ms using the Fridericia formula. Patients with known active HIV, hepatitis B, or hepatitis C infection were ineligible. All patients provided informed consent for participation in the clinical trial. The study was approved by the Institutional Review Board and conducted in accordance with the principles of the Declaration of Helsinki.

Study treatment

Patients were treated in a dose-escalation cohort with two dose levels (DL) using a Rolling 6 design and then onto

Table 1. Clinical characteristics.

Clinical characteristics	All DLBCL, N=11	PMBCL, N=5
Age in years, median (range)	51 (21-79)	34 (21-51)
Male, N (%)	5 (45)	2 (40)
Ethnicity, N (%)		
Hispanic	0 (0)	0 (0)
White	6 (55)	2 (40)
Asian	4 (36)	2 (40)
Black	1 (9)	1 (20)
Histology, N (%)		
DLBCL	4 (36)	
PMBCL	5 (45)	
Transformed DLBCL	2 (18)	
Cell-of-origin by Hans criteria, N (%)		
Non-GCB	9 (82)	4 (80)
Unknown	2 (18)	1 (20)
Stage 3-4, N (%)	4 (36)	3 (60)
Extranodal involvement, N (%)	5 (45)	2 (40)
Primary refractory, N (%)	7 (64)	4 (80)
Refractory to most recent therapy, N (%)	10 (91)	5 (100)
IPI Score, N (%)		
Low risk (0-1)	5 (45)	2 (40)
Low-intermediate risk (2)	6 (55)	3 (60)
Double-expressor, N (%)		
Yes	4 (36)	0 (0)
No	5 (45)	4 (80)
Unknown	2 (18)	1 (20)
Double-hit, N (%)		
Yes	1 (9)	1 (20)
No	8 (73)	3 (60)
Unknown	2 (18)	1 (20)
Prior CAR T-cell therapy, N (%)	3 (21)	1 (20)

Clinical characteristics	FL, N=9
Age in years, median (range)	60 (28-78)
Male, N (%)	8 (89)
Ethnicity, N (%)	
Hispanic	2 (22)
White	7 (78)
Asian	2 (22)
Grade, N (%)	
2	6 (67)
3A	3 (33)
Stage 3-4, N (%)	6 (67)
Extranodal involvement, N (%)	3 (33)
Refractory to most recent therapy, N (%)	5 (56)
Rituximab-resistant, N (%)	9 (100)
Double-refractory*, N (%)	9 (100)
FLIPI score category, N (%)	
Good (0-1)	4 (44)
Intermediate (2)	2 (22)
Poor (3-5)	3 (33)

Best response	FL, N=9	DLBCL, N=11	Non-PMBL DLBCL, N=6	PMBL, N=5
Cycles, median (range)	4 (2-16)	5 (1-35)	3 (1-32)	32 (1-35)
Complete response, N (%)	1 (11)	5 (45)	1 (17)	4 (80)
Partial response, N (%)	1 (11)	1 (9)	1 (17)	0 (0)
Stable disease, N (%)	6 (67)	2 (18)	2 (33)	0 (0)
Progressive disease, N (%)	1 (11)	3 (27)	2 (33)	1 (20)

*Double-refractory indicates refractory to rituximab and an alkylating chemotherapy. DLBCL: diffuse large B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; GCB: germinal center B cell; CAR: chimeric antigen rector; IPI: International Prognostic Index; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index.

an expansion cohort with treatment at the recommended phase II dose (RP2D). In DL1, vorinostat was administered orally at 100 mg twice daily on days 1-5 and 8-12 and in DL2, vorinostat was administered at 200 mg twice daily on days 1-5 and 8-12. Pembrolizumab dose was 200 mg intravenously (IV) on day 1; the cycle length was 21 days. Treatment could continue for a maximum of 2 years. Patients with disease progression could continue on therapy at the discretion of the principal investigator provided that there were no signs or symptoms of progressive disease, no decline in Eastern Cooperative Oncology Group performance status, and absence of progressive tumor at critical anatomical sites requiring urgent medical intervention.

Study assessment and endpoints

Safety was monitored continuously with toxicities assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Dose-limiting toxicity (DLT) was assessed in the first two cycles. DLT was defined as any of the following at least possibly related to study treatment: grade 4 neutropenia lasting >7 days, grade 4 thrombocytopenia lasting >7 days or requiring platelet transfusion, grade 3 or 4 thrombocytopenia associated with grade 2 or higher bleeding, grade 4 anemia not associated with lymphoma, grade ≥3 pneumonitis that does not resolve to grade ≤1 within 3 days after initiation of supportive care measures, any clinically relevant grade 3 or grade 4 non-hematologic AE with certain exceptions, and any grade 5 AE. Positron emission tomography/computed tomography (PET/CT) scans were performed at baseline and then every four cycles until disease progression or off-study therapy; a diagnostic quality CT with IV contrast was acceptable if a CR was previously confirmed by PET/CT. Responses were assessed by investigators according to the 2014 Lugano Classification.[27] The primary endpoints were safety, tolerability, and determination of the RP2D. Secondary endpoints included the CR rate, duration of response (DOR), OS, and PFS. For DOR and PFS, failures included disease relapse/progression or death due to any cause. DOR/PFS were censored at the last follow-up or start of other non-protocol therapy, whichever occurred earlier.

Trial design and statistical considerations

Dose escalation followed a Rolling 6 design.[28] Maximum tolerated dose (MTD) was defined as the highest dose level with at most one out of six participants with DLT; RP2D would be at or lower than MTD. Participants evaluable for DLT during dose escalation needed to complete treatment through DLT period (2 cycles), receive the planned pembrolizumab dose and miss <30% vorinostat doses during DLT period, except due to DLT. DOR, PFS and OS were estimated based on Kaplan-Meier product limit method with Greenwood variance estimator and along with confidence interval (CI) estimated based on log-log transformation.

Correlative analyses

PD-L1 protein expression was assessed by immunohistochemistry (IHC) (SP263 clone) using an H-score system, and *PD-L1* gene alterations were identified using fluorescent *in situ* hybridization as previously described.[18]

Results

Patients

Twenty patients with FL, DLBCL, or PMBL were enrolled and received study therapy. Baseline characteristics are listed in Table 1. Of the 20 patients enrolled, nine had a diagnosis of FL and 11 had DLBCL. Of the 11 DLBCL patients, five had PMBL. Thirteen (65%) patients were male and the median age was 59 years (range, 21-79). The median number of prior lines of therapy were three (range, 1-7 prior lines). A large proportion of patients exhibited high-risk features, including 15 (75%) who were refractory to their most recent line of therapy, three (15%) who progressed after prior CAR T-cell therapy, and four (20%) who progressed after prior BsAb therapy.

Treatment disposition and safety

All 20 patients received at least one dose of treatment and were evaluable for safety endpoints. A median number of four cycles of therapy were administered (range, 1-35 cycles), and all subjects have discontinued treatment. Reasons for treatment discontinuation included: disease progression/insufficient response/stable disease (n=12, 60%), toxicity (n=3, 15%), completion of study treatment (n=2, 10%), discontinuation of study treatment while in CR (n=1, 5%), proceeding to consolidative stem cell transplant (n=1, 5%), and patient preference (n=1, 5%).

On the entire study (including cHL patients not included in this report), two subjects experienced a DLT during the dose escalation portion of the study (6 each treated at DL1 and DL2), both had FL. One patient experienced a grade 3 Stevens-Johnson syndrome (SJS) at DL1, and one patient experienced a DLT of grade 3 pulmonary embolism at DL2. Therefore, DL2 (200 mg vorinostat twice daily and 200 mg pembrolizumab) was established as the RP2D for the dose expansion cohort. The most common adverse events (AE) among the 20 NHL patients treated on the study (DL1 or DL2) are listed in Table 2. These included hypertension (70%), diarrhea (65%), nausea (65%), fatigue (60%), leukopenia (60%), and anemia (55%). Grade ≥3 AE included neutropenia (15%), lymphopenia (10%), mucositis (5%), hyperkalemia (5%), hypertension (5%), pulmonary embolism (5%), anemia (5%), and leukopenia (5%). Immune-related AE among NHL patients included the patient with SJS. Three other patients experienced grade 1-2 immune-related hypo- and/or hyper-thyroidism. There were three patients with a delay of pembrolizumab, one patient discontinued vorinostat for grade 2 nausea and anorexia, and one patient had a vori-

nostat dose reduction from 200 mg twice daily to 100 mg twice daily due to abdominal cramping. The patient with extensive mucocutaneous SJS was treated with high-dose corticosteroids without resolution. Infliximab and cyclosporine were also used, but the patient died of invasive fungal infection due to the extensive immunosuppression used to treat the ongoing SJS.

Efficacy and correlatives

Among all 20 patients, the ORR and CR were 8 and 20 (40%) and 6 and 20 (30%), respectively. Individual response characteristics by disease subtype are shown in Table 1 and Figure 1. The disease-specific CR and ORR were 1 and 9 and 2 and 9 (11% and 22%) for FL; 5 and 11 and 6 and 11 (45% and 55%) for all DLBCL; and 4 and 5 and 4 and 5 (80% and 80%) for PMBL. Disease control rates (CR, PR, and SD) were 89% for FL, 73% for all DLBCL, and 80% for PMBL. Among the three patients who received prior CAR T-cell therapy, there were one CR and two PD; among the four patients with prior BsAb therapy, there were one CR and three SD. Of the two patients achieving CR after prior CAR T-cell or BsAb therapy, one had PMBL with a best response of stable disease to prior Liso-cel CAR T. The patient achieved a CR to pembrolizumab plus vorinostat and then proceeded to a consolidative allogeneic stem cell transplant after five cycles on study and remains in ongoing remission after approximately 4 years. The second CR patient had FL and progressed after prior CD20 BsAb. This patient remained in CR on study before progression after 12 cycles and off-treatment after 16 cycles. The patient subsequently had a brief response to CAR T-cell therapy and was then lost to follow up.

Seven subjects have died as of the data cutoff with a median follow-up of 3.8 years (range, 2.9-5.1) among the survivors. The most common cause of death was disease progression (n=5, 2 FL and 3 DLBCL). One FL patient died from pulmonary fungal infection approximately 3 months after coming off study treatment, and another FL patient died approximately 10 months after off-study treatment and cause of death was unavailable. Four subjects started other therapy without disease progression and therefore were censored for PFS/DOR, three of them were SD on treatment and the fourth was a CR patient who went to transplant.

Median PFS and DOR were 8.0 (95% CI 2.5-25.0) and 22.3 (95% CI: 0.6-not available) months for the total NHL population (Figure 2). Disease-specific median PFS were 4.0 months (95% CI: 2.1-12.5) for FL, 8.2 months (95% CI: 0.7-not available) for all DLBCL, and not reached amongst the PMBL patients. DOR were 0.6 and 2.8 months for the 2 FL responders, and median DOR was not reached for all patients with DLBCL, including PMBL. Median OS was not reached for the population overall nor for any subset. The 2-year PFS was 29.0% (95% CI: 9.7-52.0) overall, 0% for FL, 49.1% (95% CI: 16.7-75.3) for all DLBCL, and 80%

Table 2. Adverse events with an attribution of possibly or higher.

All grades (>10%)	N (%)
Hypertension	14 (70)
Diarrhea	13 (65)
Nausea	13 (65)
Fatigue	12 (60)
White blood cell decreased	12 (60)
Anemia	11 (55)
Abdominal pain	10 (50)
Neutrophil count decreased	10 (50)
Vomiting	8 (40)
Hyponatremia	8 (40)
Platelet count decreased	7 (35)
Anorexia	7 (35)
Dyspepsia	6 (30)
Myalgia	6 (30)
Constipation	5 (25)
Creatinine increased	5 (25)
Hypermagnesemia	5 (25)
Hypophosphatemia	5 (25)
Lymphocyte count decreased	5 (25)
Weight loss	5 (25)
Hypocalcemia	4 (20)
Headache	4 (20)
Dehydration	4 (20)
Rash maculopapular	4 (20)
Hyperkalemia	3 (15)
Dizziness	3 (15)
Hypoalbuminemia	3 (15)
Fever	3 (15)
Sinus tachycardia	3 (15)
Chills	3 (15)
Sore throat	3 (15)
Malaise	3 (15)
Grade 3+	**N (%)**
Neutrophil count decreased	3 (15)
Lymphocyte count decreased	2 (10)
Mucositis oral	1 (5)
Hyperkalemia	1 (5)
Hypertension	1 (5)
Thromboembolic event	1 (5)
Anemia	1 (5)
White blood cell decreased	1 (5)

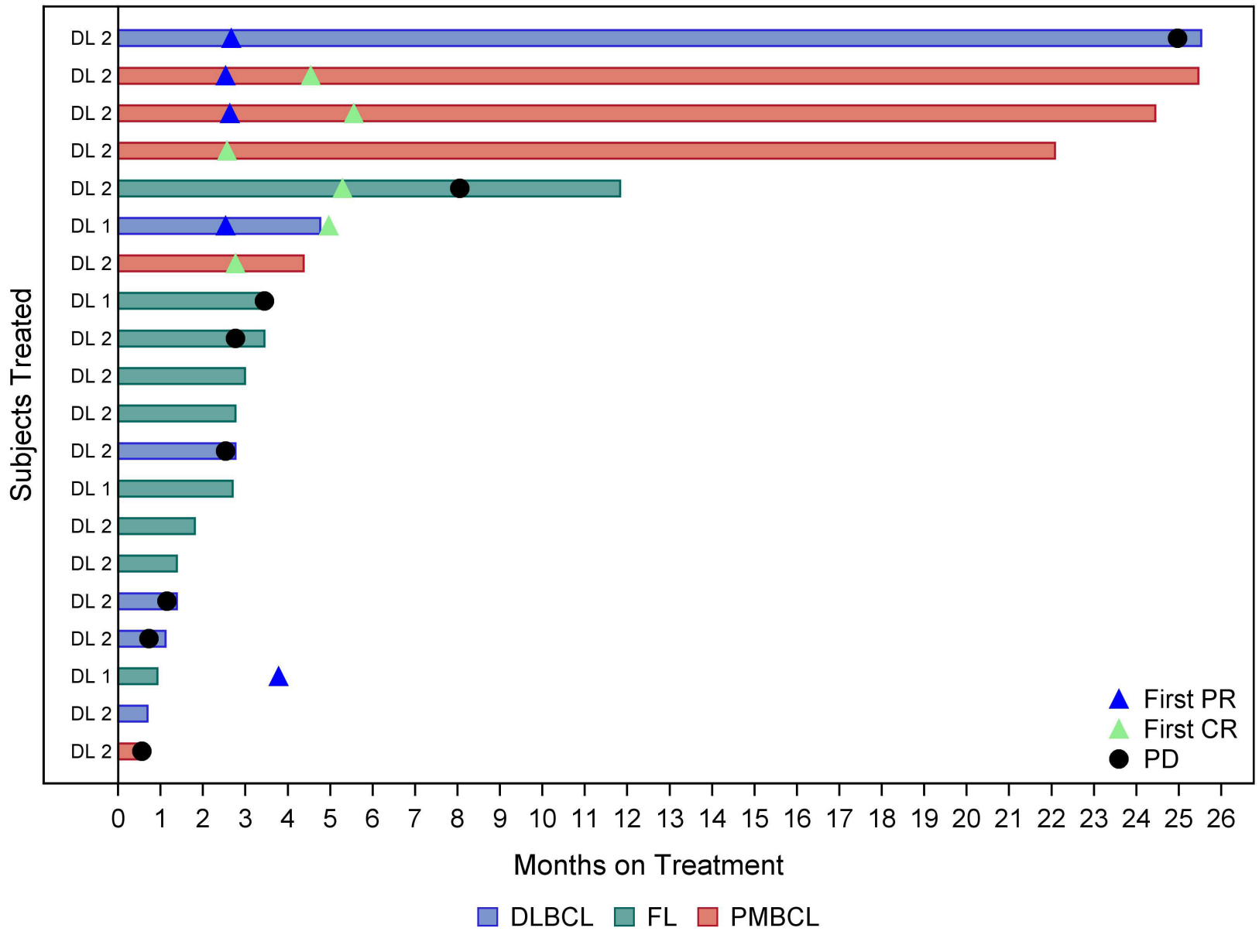

Figure 1. Response characteristics. Swimmer plot demonstrating response characteristics to pembrolizumab with vorinostat. Of note, 1 follicular lymphoma patient discontinued treatment after 1 month of therapy due to toxicity, but remained on study and achieved a partial response (PR). CR: complete response, PD: progressive disease, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma; PMBCL: primary mediastinal B-cell lymphoma.

(95% CI: 20.4-96.9) for PMBL. The 2-year OS was 65.0% (95% CI: 40.3-81.5) overall, 55.6% (95% CI: 20.4-80.5) for FL, 72.7% (95% CI: 37.1-90.3) for all DLBCL, and 100% for PMBL.

We performed PD-L1 immunohistochemistry and *PD-L1* fluorescence *in situ* hybridization on archived tumor samples and assessed association between *PD-L1* expression, 9p24.1 alterations, and response to treatment. Eight patients had samples available for correlative testing (5 DLBCL and 3 PMBL). All three PMBL patients had PD-L1 gene amplifications, and two of these cases demonstrated intense PD-L1 protein expression on tumor cells (*Online Supplementary Table S1; Online Supplementary Figure S1*). All three of these patients achieved a CR to pembrolizumab plus vorinostat. Among the five non-PMBL DLBCL cases, there were no PD-L1 amplifications or *PD-L1* copy gains. *PD-L1* protein expression was modest or low in all cases, and was not associated with response. Interestingly, the DLBCL patient achieving a 2-year remission was Epstein-Barr virus-positive as assessed by EBER *in situ* hybridization staining.

Discussion

In this phase I study of pembrolizumab and vorinostat in patients with r/r B-cell NHL, we observed objective responses in highly refractory patients, with particularly notable preliminary activity in PMBL. The combination of vorinostat and pembrolizumab exhibited only modest clinical activity in FL or in non-PMBL DLBCL (ORR: 22% and 33%, respectively). The combination was however well-tolerated in most patients. The RP2D was determined to be 200 mg twice daily of vorinostat on days 1-5 and 8-12 in combination with 200 mg of pembrolizumab on day 1 of each 3-week cycle. There was a low incidence of grade ≥3 AE with this dosing schedule, and the overall safety profile was consistent with the known single-agent toxicities of each drug. Side effects were primarily related to hypertension, hematological, and gastrointestinal toxicities, and were largely manageable with a low rate of treatment discontinuation.

In our study, we noted a high ORR and CR rate to pembrolizumab with vorinostat in PMBL. The 80% CR rate we observed in PMBL patients compares favorably to the

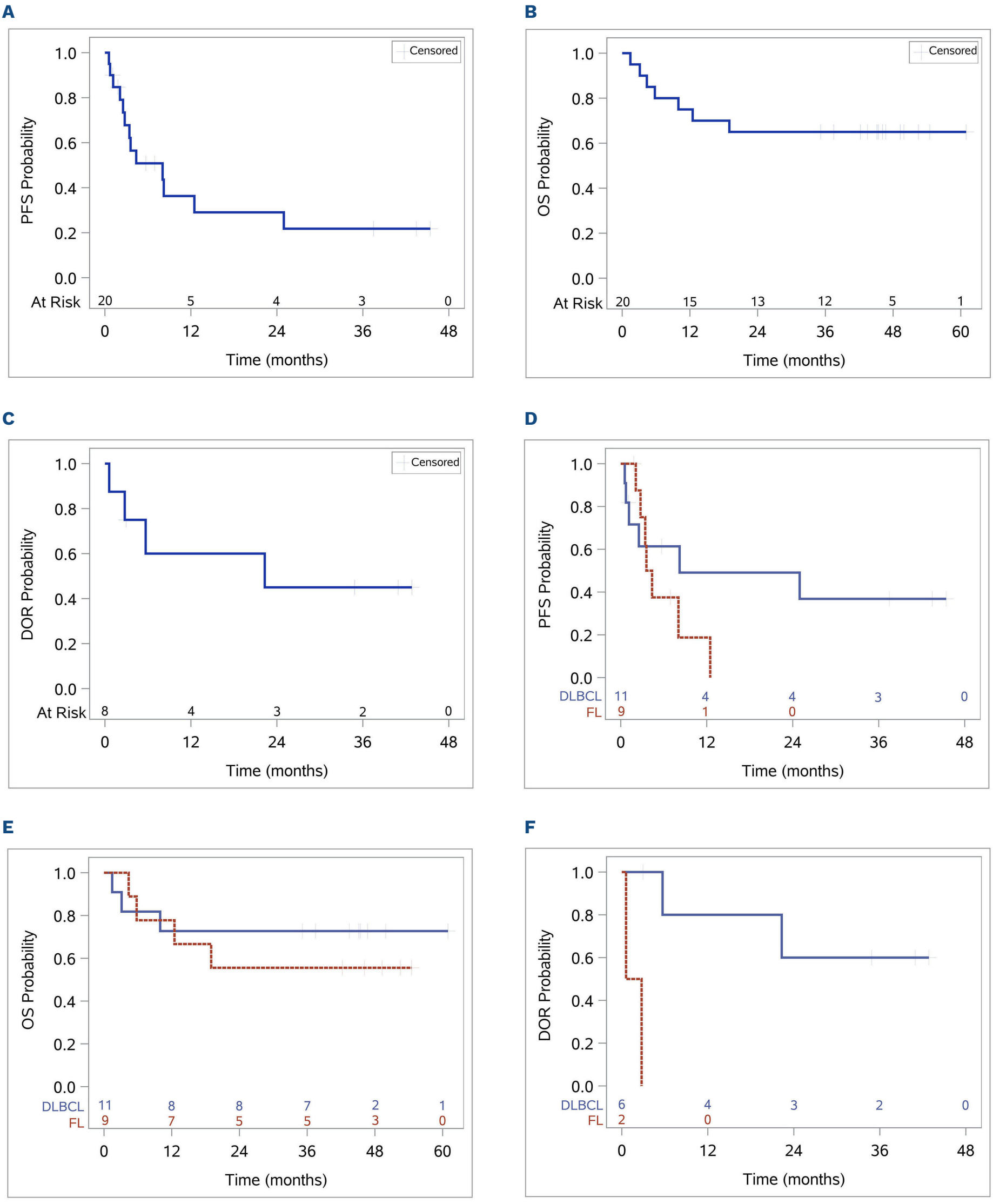

Figure 2. Survival outcomes. (A) Progression-free survival (PFS), (B) overall survival (OS) and (C) duration of response (DOR) to pembrolizumab with vorinostat. (D) PFS, (E) OS and (F) DOR stratified by follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).

reported data of pembrolizumab monotherapy where CR rates were noted to only be 19% in a combined phase I/II study of 74 PMBL patients.[17] Achieving a CR to PD-1-based treatment in PMBL appears to be an especially important milestone because all PMBL patients achieving a CR on the aforementioned phase I/II study of pembrolizumab remain in remission.[17] Similarly durable responses were observed in our study as well as a study of nivolumab plus brentuximab vedotin.[29] While there were only five PMBL patients enrolled on our study and our findings would require validation in a larger cohort, the high CR rate is nonetheless an encouraging early signal of activity in PMBL based on our similar findings of encouraging activity in heavily treated cHL, a disease that shares biological features with PMBL.[30–32] In particular, PMBL and cHL are both JAK/STAT-driven tumors that frequently exhibit intense PD-L1 expression as the result of gene amplifications and activating translocations occurring within the *CD274* (PD-L1) locus.[33,34] Thus, adding vorinostat to PD-1 blockade may be a particularly useful method by which to improve the efficacy of anti-PD-1 monotherapy in strongly PD-L1$^+$ lymphomas such as cHL, PMBL, and certain subsets of DLBCL.[18,33–35]

Interestingly, other epigenetic modifying therapies have also demonstrated robust clinical responses when combined with PD-1 blockade in cHL. In particular, combining the DNMT3A inhibitor, decitabine, with PD-1 blockade is associated with high CR and ORR in PD-1 refractory cHL,[26,36] and the combination significantly improves CR rates and PFS compared to anti-PD-1 monotherapy in anti-PD-1 naïve patients.[25] Combining DNMT3A inhibitors with PD-1 blockade may, therefore, represent a promising treatment strategy in PMBL and other strongly PD-L1$^+$ NHL given the biological similarities between cHL and PMBL noted above. Moreover, these data suggest that epigenetic modifying therapies should be explored further in combination with PD-1 blockade in PD-L1$^+$ lymphomas, either in novel combinations (e.g., HDACi + DNTM3Ai + anti-PD-1) or during earlier lines of therapy (e.g., elderly/frail patients or as a bridge to consolidative cellular therapy or stem cell transplantation). Alternatively, pembrolizumab plus vorinostat could also be evaluated in PD-L1$^+$ lymphomas relapsing after CAR T-cell therapy, as this represents a growing patient population in need of improved treatment options as their expected median survival is only 5.2 months.[9] Lastly, future correlative analyses should investigate the mechanisms by which DNMT3Ai and HDACi enhance the efficacy of anti-PD-1 therapies in lymphoma and whether those mechanisms are potentially complementary in action.

While the clinical outcomes of pembrolizumab plus vorinostat are promising in PMBL, the combination exhibited only modest activity in FL and non-PMBL DLBCL. Collectively, the CR and ORR of pembrolizumab with vorinostat were only 13% and 26% in these NHL subtypes, respectively. These data suggest only a marginal incremental benefit compared to historical data of anti-PD-1 monotherapy where ORR are 4-10%.[14,15] Together, our results contribute to a growing number of negative studies evaluating PD-1-based combinations in DLBCL and FL. These include studies evaluating PD-1 blockade in combination with other immune checkpoint inhibitors,[37] BTK inhibitors,[38] as well as with CAR T-cell therapy.[39] Thus, future efforts investigating anti-PD-1 therapies in these diseases should have strong scientific merit or restrict inclusion to PD-L1$^+$ cases that may have increased sensitivity to PD-1-based therapy. Moreover, the results of these studies provide an important lesson for the field on clinical trial development, as numerous negative PD-1 combination trials have now been developed in FL and DLBCL based on the results of early anti-PD-1 trials that included only small numbers of patients.[40] Thus, while accelerating drug development is critical to advancing the field and improving treatment options for our patients, we should ideally wait for more mature efficacy results from larger datasets before allocating significant resources to study a novel therapy.

In summary, the combination of pembrolizumab with vorinostat is safe in r/r B-cell NHL and elicits objective responses in patients with highly refractory disease. Particularly high rates of durable CR in PMBL support further investigation of this treatment regimen in this specific patient population, both in the PD-1 naïve and PD-1 refractory settings.

Disclosures

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Contributions

AFH, SP and RC conceived the study design. JG, AFH, MM and LC analyzed the data. JG, AFH and LC wrote the manuscript. AFH, LC and JG collected, assembled and interpreted the data. MM, EB, SA, SP, LN, RC, SD, NK, LP, STR, SJF, LLP, LWK, JS and VB collected and assembled the data, interpreted the data, and revised the manuscript.

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Data-sharing statement

Data used to support the findings of this study are available from the corresponding author upon request.

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