Author/s:
Foss, FM;Kim, YH;Prince, HM;Akilov, OE;Querfeld, C;Seminario-Vidal, L;Fisher, DC;Kuzel, TM;Yannakou, CK;Geskin, LJ;Feldman, T;Sokol, L;Allen, PB;Dang, NH;Cabanillas, F;Wong, HK;Ooi, CE;Xing, D;Sauter, N;Singh, P;Czuczman, M;Duvic, M

Title:
Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma

Date:
2025-04-01

Citation:
Foss, F. M., Kim, Y. H., Prince, H. M., Akilov, O. E., Querfeld, C., Seminario-Vidal, L., Fisher, D. C., Kuzel, T. M., Yannakou, C. K., Geskin, L. J., Feldman, T., Sokol, L., Allen, P. B., Dang, N. H., Cabanillas, F., Wong, H. K., Ooi, C. E., Xing, D., Sauter, N. ,... Duvic, M. (2025). Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma. Journal of Clinical Oncology, 43 (10), pp.1198-1209. https://doi.org/10.1200/JCO-24-01549.

Persistent Link:
https://hdl.handle.net/11343/355964

Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma

Francine M. Foss, MD[1]; Youn H. Kim, MD[2]; H. Miles Prince, MD, FRACP, FRCPA[3]; Oleg E. Akilov, MD, PhD[4]; Christiane Querfeld, MD, PhD[5]; Lucia Seminario-Vidal, MD, PhD[6,7]; David C. Fisher, MD[8]; Timothy M. Kuzel, MD, FACP[9,10]; Costas K. Yannakou, PhD, MBBS (Hons), FRACP, FRCPA[11,12]; Larisa J. Geskin, MD, FAAD[13]; Tatyana Feldman, MD[14]; Lubomir Sokol, MD, PhD[15]; Pamela Blair Allen, MD[16]; Nam Hoang Dang, MD, PhD[17]; Fernando Cabanillas, MD[18]; Henry K. Wong, MD, PhD[19]; Chean Eng Ooi, PhD[20]; Dongyuan Xing, PhD[21]; Nicholas Sauter, MD[20]; Preeti Singh, MD[21]; Myron Czuczman, MD[21]; and Madeleine Duvic, MD[22]

DOI https://doi.org/10.1200/JCO-24-01549

ABSTRACT

PURPOSE Denileukin diftitox (DD)-cxdl is a fusion protein comprising diphtheria toxin fragments A and B and human interleukin-2. This phase III, multicenter, open-label, single-arm registrational trial evaluated the efficacy and safety of DD-cxdl in patients with relapsed/refractory (R/R) cutaneous T-cell lymphoma (CTCL).

PATIENTS AND METHODS In the main study, which followed a dose-finding lead-in, DD-cxdl was administered intravenously daily (5 days; 9 μg/kg/d once daily) every 21 days for up to eight cycles. Patients in the primary efficacy analysis set (PEAS) were required to have stage IA-IIIB CTCL (mycosis fungoides and/or Sézary syndrome) and at least ≥one previous systemic therapy. The primary efficacy end point was objective response rate (ORR) using the Global Response Score. Secondary end points were duration of response (DOR), time to response (TTR), skin tumor burden, and safety and tolerability.

RESULTS The PEAS included 69 patients (median age, 64.0 years). The ORR was 36.2% (95% CI, 25.0 to 48.7), including 8.7% with complete response. The median DOR was 8.9 months (95% CI, 5.0 to not estimable), and the median (Q1-Q3) TTR was 1.4 (0.7-2.1) months. A total of 84.4% of patients showed decreased skin tumor burden, with 48.4% showing a ≥50% decrease. Treatment-emergent adverse events (TEAEs) of special interest, most of which were grade 1 or 2, included infusion reaction (73.9%), hypersensitivity (68.1%), hepatotoxicity (36.2%), and capillary leak syndrome (20.3% [grade ≥3, 5.8%]). Other common TEAEs were nausea (43.5%) and fatigue (31.9%).

CONCLUSION Efficacy and safety results show that DD-cxdl would potentially fulfill a serious, unmet medical need for patients with R/R CTCL.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

Accepted November 12, 2024

Published December 19, 2024

J Clin Oncol 43:1198-1209

View Online Article

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a rare form of lymphoma accounting for approximately 4% of all non-Hodgkin lymphomas.[1,2] CTCL has multiple clinical variants, most commonly mycosis fungoides (MF; approximately 60% of cases)[3] and less commonly Sézary syndrome (SS; 3%-5% of cases).[3-6] MF and SS share many clinical and pathophysiologic features,[7] and prognosis is based on the extent of disease.[8] Stage IA/IB disease is typically indolent for several years without affecting life expectancy.[9,10] However, approximately 30% of patients advance to higher stages within 10 years, with the median overall survival declining to 4.7 years in stage IIB (tumor), 3.4 years in stage IIIB (erythroderma), and 1.4 years in stage IVB (nodal and visceral) disease.[8-11]

CTCL treatment aims to clear or improve lesions, control symptoms, and minimize progression while avoiding toxicity.[12] Stage IA-IIA disease control is typically achieved with skin-directed therapies (topical agents, phototherapy, radiation). Systemic therapy, often combined with skin-directed therapy, is recommended for advanced-stage disease (stage IIB and onward).[6] However, patients with advanced disease inevitably relapse within months of achieving a response.[6,12] In addition, systemic therapies

CONTEXT

Key Objective

This phase III, single-arm registrational trial evaluated the efficacy and safety of denileukin diftitox (DD)-cxdl (a fusion protein comprising diphtheria toxin fragments A and B and human interleukin-2) in patients with relapsed/refractory (R/R) cutaneous T-cell lymphoma (CTCL).

Knowledge Generated

This study confirms the efficacy and tolerability of DD-cxdl in heavily pretreated patients with stage IA-IIIB R/R CTCL, with an objective response rate of 36.2%, a time to response of 1.4 months, a median duration of response of 8.9 months, and a tolerable safety profile.

Relevance *(J.W. Friedberg)*

These results demonstrate that DD-cxdl represents a therapeutic option for patients with R/R CTCL and led to US Food and Drug Administration approval in August 2024. Future studies should explore biomarkers of response with a goal to enable a precision approach to treatment of this challenging disease.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

carry the risk of cumulative toxicity and the development of resistance.[6,12-14] There remains a need for safe and effective therapies that offer durable response for patients with advanced-stage relapsed/refractory (R/R) CTCL.[12]

Denileukin diftitox (DD) is a recombinant cytotoxic fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met1-Thr387)-His and human interleukin-2 (IL-2; Ala1-Thr133). On binding to IL-2 receptors on the cell surface, DD is internalized by receptor-mediated endocytosis. The fusion protein is subsequently cleaved, releasing diphtheria toxin moieties of the protein, which results in protein synthesis inhibition and, ultimately, cell death.[15-17] DD has shown clinical antitumor activity against a range of tumor types expressing the IL-2 receptor (eg, CTCL)[15,16] and antineoplastic effects against tumors via transient depletion of immunosuppressive IL-2 receptor-expressing regulatory T cells.[18,19]

DD was marketed in the United States as ONTAK (1999-2014), indicated for patients with R/R CTCL with malignant cells expressing the CD25 component of the IL-2 receptor.[20] The US Food and Drug Administration (FDA) approval for DD included a requirement to improve manufacturing processes to increase product purity.[21] DD-cxdl (formerly known as E7777) is the same recombinant protein as historical DD, but reformulated with improved purity and bioactivity (approximately 1.5-2 times greater specific bioactivity in nonclinical assays). DD-cxdl has an increased percentage of active protein monomer species, with a concomitant decrease in misfolded protein and protein aggregates.[22] The efficacy and safety of DD-cxdl were demonstrated in a Japan single-arm, phase II study in patients with R/R peripheral T-cell lymphoma or CTCL,[23] leading to the marketing approval of DD-cxdl in Japan in 2021 for these indications.[24]

In the United States, the FDA approved DD-cxdl (LYMPHIR; Citius Oncology Inc; Cranford, NJ) on August 7, 2024, for the treatment of adult patients with R/R stage I-III CTCL after ≥one previous systemic therapy.[25] Approval was based on an FDA-required registrational pivotal trial for DD-cxdl, with a similar patient cohort as the original DD pivotal trial.[26] We present results from the phase III, multicenter, open-label, single-arm registrational trial (ClinicalTrials.gov identifier: NCT01871727), conducted to evaluate the efficacy and safety of DD-cxdl in patients with R/R CTCL.

PATIENTS AND METHODS

Trial Design and Oversight

The study was conducted in the United States (17 sites) and Australia (three sites) and consisted of an initial lead-in period, followed by the main study (Fig 1). The lead-in aimed to establish the maximum tolerated dose (MTD) and select the dose for use in the main study.[27] Lead-in patients who received DD-cxdl at the dose selected for the main study were pooled with main study patients for the final efficacy and safety analyses.

All study design elements were developed in consultation with the FDA[28] and performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and all applicable local Good Clinical Practice guidelines and regulations. Approval was obtained from Institutional Review Board(s) or Independent Ethics Committees, as appropriate (Data Supplement, Table S1, online only). All patients provided written informed consent.

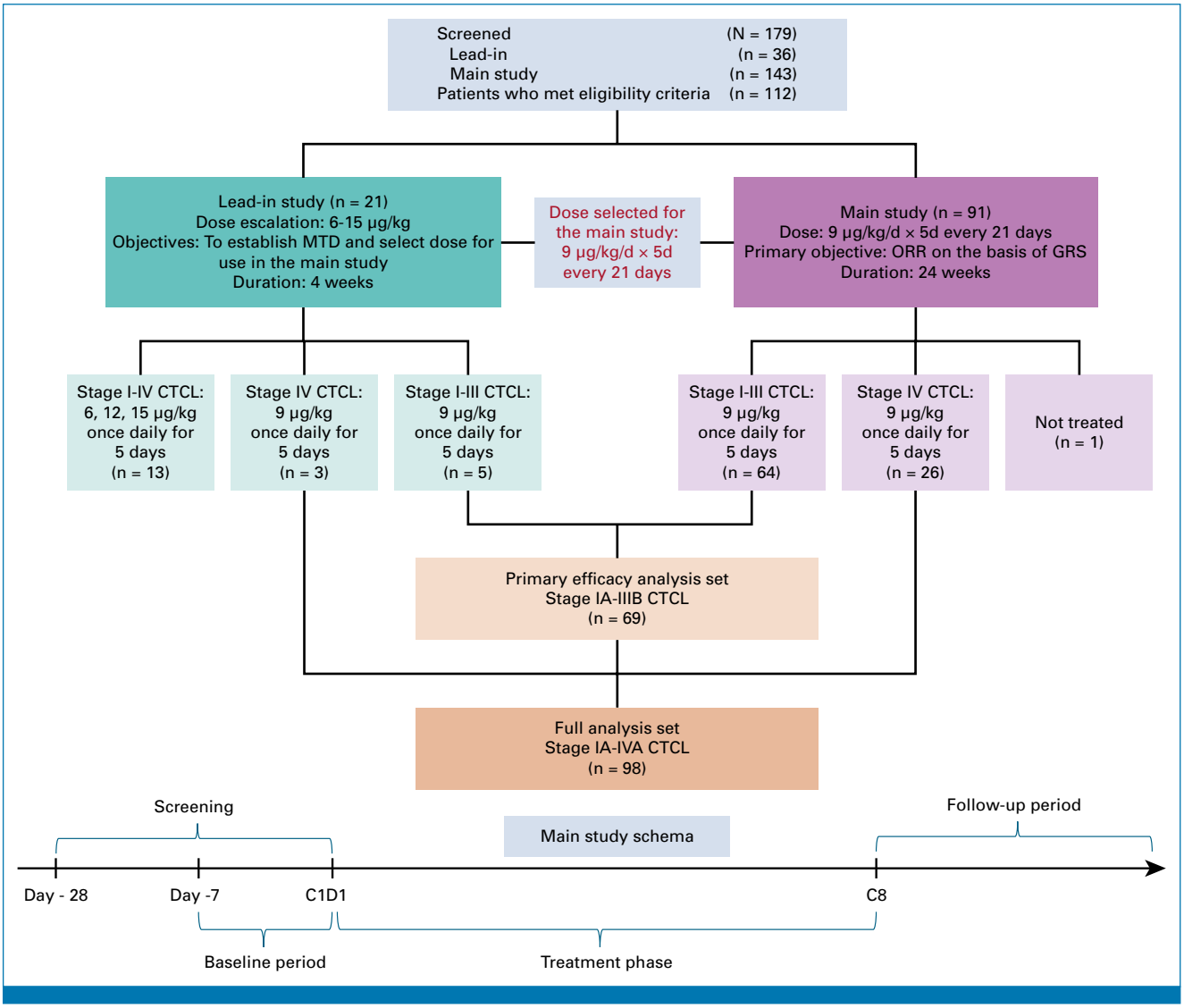

FIG 1. Study design. The lead-in study included patients with stage IA-IVB CTCL. The main study included patients with stage IA-IVA CTCL; however, the main study inclusion criteria were later amended to exclude all stage IV patients and include only stage IA-IIIB to match the patient population in historical reference study of denileukin diftitox (ie, Prince et al).[26] Enrollment in the main study commenced after ≥one objective investigator assessment was recorded and the MTD was established. The main study comprised three phases: pretreatment, treatment, and extension. The pretreatment phase included the screening and baseline periods. The screening period was from day −28 to treatment initiation (C1D1); during this time, informed consent was obtained, and eligibility criteria were ascertained for all patients. The baseline period was from day −7 to treatment initiation. The treatment phase included the treatment and follow-up periods. The follow-up period included tumor assessment until treatment discontinuation because of PD. The extension phase started after primary data analysis cutoff and includes follow-up data only. A sample size of approximately 70 stage I-III patients was estimated assuming that the lower limit of the two-sided 95% CI of ORR exceeding 25% indicates clinical benefit in persistent and recurrent CTCL, as per FDA guidance. C, cycle; CTCL, cutaneous T-cell lymphoma; D, day; FDA, US Food and Drug Administration; GRS, Global Response Score; MTD, maximum tolerated dose; ORR, objective response rate; PD, progressive disease.

Main Study Objectives and End Points

The overall objective was to demonstrate the efficacy of DD-cxdl in patients with stage IA-IIIB R/R CTCL. A single-arm design using objective response rate (ORR) for regression of measurable disease as the primary end point (on the basis of the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer Global Response Score [GRS] criteria)[29] was considered appropriate and accepted for registrational purposes.[28] Objective response is complete response (CR) combined with partial response (PR), measured using the GRS. GRS is a composite of diseases in skin, lymph nodes, blood, and viscera.[29]

Secondary end points were duration of response (DOR), time to response (TTR), skin tumor burden, and safety and tolerability, including treatment-emergent adverse events (TEAEs) of special interest (classified on the basis of clinical experience

TABLE 1. Demographic and Baseline Characteristics, Disease History, and Previous Anticancer Therapy

Category	PEAS (n = 69)	FAS (n = 98)
Age, years, median[a]	64.0	65.0
Male, No. (%)	45 (65.2)	61 (62.2)
Female, No. (%)	24 (34.8)	37 (37.8)
Race,[b] No. (%)		
White	50 (72.5)	73 (74.5)
Black or African American	13 (18.8)	16 (16.3)
Asian	1 (1.4)	1 (1.0)
Ethnicity, No. (%)		
Hispanic or Latino	10 (14.5)	14 (14.3)
Not Hispanic or Latino	57 (82.6)	81 (82.7)
Missing	2 (2.9)	3 (3.1)
ECOG performance status, 0, No. (%)	39 (56.5)	53 (54.1)
ECOG performance status, 1, No. (%)	30 (43.5)	45 (45.9)
CTCL type, No. (%)		
MF	66 (95.7)	74 (75.5)
SS	3 (4.3)	24 (24.5)
CTCL disease staging, No. (%)		
IA/IB/IIA	30 (43.5)	30 (30.6)
IIB	24 (34.8)	24 (24.5)
IIIA/IIIB	15 (21.7)	15 (15.3)
IVA/IVA_1/IVA_2/IVB[c]	—	29 (29.6)
Patients with any previous anticancer therapy,[d] No. (%)	69 (100.0)	98 (100.0)
Mean (SD)	4.8 (2.99)	5.1 (3.03)
Median (Q1-Q3)	4.0 (3.0-7.0)	4.0 (3.0-7.0)
Min-max	1-18	1-18
1-2	13 (18)	15 (15)
3-4	26 (24)	37 (38)
5-7	18 (26)	26 (27)
8+	12 (17)	20 (20)
Type of nonmedication anticancer therapy,[e] No. (%)		
Photodynamic therapy[f]	39 (56.5)	62 (63.3)
TSEBT	29 (42.0)	37 (37.8)
Chemotherapy: topical	20 (29.0)	26 (26.5)
Radiation: local	19 (27.5)	25 (25.5)
Allogenic stem-cell transplantation	1 (1.4)	2 (2.0)
Type of systemic anticancer therapy,[e] No. (%)		
Retinoid	34 (49.3)	51 (52.0)
Methotrexate/pralatrexate	34 (49.3)	43 (43.9)
HDAC inhibitor	24 (34.8)	48 (49.0)
Immune therapy: interferon	23 (33.3)	37 (37.8)
Brentuximab vedotin	18 (26.1)	28 (28.6)
Immune therapy: other	14 (20.3)	28 (28.6)
Chemotherapy: other systemic	12 (17.4)	23 (23.5)
Mogamulizumab	8 (11.6)	10 (10.2)
Type of other anticancer therapy,[e] No. (%)		
Investigational	13 (18.8)	16 (16.3)
Other[g]	7 (10.1)	10 (10.2)

NOTE. Percentages are based on the total number of patients in the relative treatment group.

Abbreviations: CTCL, cutaneous T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ECP, extracorporeal photopheresis; FAS, Full Analysis Set; HDAC, histone deacetylase; IEAS, Investigator Efficacy Analysis Set; IRC, independent review committee; max, maximum; MF, mycosis fungoides; min, minimum; PEAS, primary efficacy analysis set; PUVA, psoralen ultraviolet light A; Q, quartile; SD, standard deviation; SS, Sézary syndrome; TSEBT, total skin electron beam therapy; UVB, ultraviolet light B.

[a]Age was calculated at the date of informed consent.

[b]In the PEAS, there were one patient with race missing and four patients with race in the category of Other. In the FAS, there were one patient with race missing and seven patients with race in the category of Other.

[c]CTCL disease staging was performed for all patients by the investigator at screening. The PEAS comprised 69 patients determined to have stage IA-IIIB CTCL at baseline. Two additional patients were classified as stage IA-IIIB at baseline by investigators but were determined to have visceral disease at baseline by IRC review. These two patients were effectively considered stage IVB but were kept in the study and included in the FAS (n = 98) and IEAS (n = 71) but not in the PEAS.

[d]Including patients with medication/nonmedication.

[e]Patients may be counted in multiple categories.

[f]Photodynamic therapy includes PUVA, UVB, and ECP.

[g]Other therapy includes imiquimod, phosphatidylinositol-3-kinase inhibitor, protein kinase inhibitor, adjuvant low-dose interferon alpha, donor memory $CD8^+$ T-cell infusion, and whole-body radiation (other than TSEBT).

with historical DD).[26] DOR was defined as the time from confirmed objective response until the earliest documentation of progressive disease (PD), start of new anticancer therapy, or all-cause death. Patients without these events were censored at their last day of efficacy assessment. Progression-free survival (PFS), defined as the date of first dosing until the earliest documentation of PD or death, was analyzed as an exploratory end point. Patients without evidence of PD or death were censored at their last day of efficacy assessment.

Patient Eligibility Criteria

For both the lead-in study and the main study, all patients were required to have histopathologic diagnosis of CTCL (MF or SS) at study entry, confirmed by skin biopsy, lymph node biopsy, and/or blood assessment; CD25 assay–positive tumor by central pathology review (detectable CD25 on ≥20% of total lymphoid infiltrate in biopsied lesions by immunohistochemistry); Eastern Cooperative Oncology Group performance status 0, 1, or 2 (lead-in) or 0, 1 (main study); normal hepatic function (bilirubin ≤1.5× the upper limit of normal [ULN]; alkaline phosphatase ≤3.0 × ULN; AST and ALT ≤3.0 × ULN; albumin ≥3.0 g/dL); and documentation of previous therapy for CTCL. The lead-in study enrolled patients with stage IA-IVB CTCL, excluding individuals with central nervous system involvement. The main study enrolled patients with stage IA-IVA CTCL, excluding patients with visceral disease. Primary efficacy analyses were conducted on patients with stage IA-IIIB CTCL to match the patient population in the

TABLE 2. Tumor Response by IRC Assessment and Investigator Assessment per Olsen 2011

End Point	IRC, PEAS DD-Cxdl 9 μg/kg once daily for 5 days (n = 69)	Investigator Assessment, IEAS DD-Cxdl 9 μg/kg once daily for 5 days (n = 71)
Best overall response from GRS, No. (%)		
CR	6 (8.7)	6 (8.5)
PR	19 (27.5)	24 (33.8)
Stable disease	36 (52.2)	33 (46.5)
Progressive disease	3 (4.3)	4 (5.6)
Unknown	5 (7.2)	4 (5.6)
Objective response rate (CR + PR), No. (%)	25 (36.2)	30 (42.3)
95% CI[a]	25.0 to 48.7	30.6 to 54.6
Clinical benefit rate (CR + PR + durable stable disease), No. (%)	34 (49.3)	38 (53.5)
95% CI[a]	37.0 to 61.6	41.3 to 65.5
DOR (months)		
Patients with objective response, No.	25	30
Observed DOR		
Median	6.47	5.68
Range (min-max)	3.0+ to 23.5+	0.7+ to 26.1+
No. of patients with DOR,[b] No. (%)		
≥6 months	13 (52.0)	14 (46.7)
≥12 months	5 (20.0)	6 (20.0)
KM estimates[c]		
Median (95% CI)	8.9 (5.0 to NE)	7.6 (5.0 to NE)
Q1 (95% CI)	5.0 (4.2 to 7.0)	5.0 (4.2 to 7.0)
Q3 (95% CI)	NE (8.9 to NE)	NE (8.9 to NE)
Censored patients,[b] No. (%)	14 (56.0)	16 (53.3)
No progression, no death, or no new anticancer treatment	10 (40.0)	12 (40.0)
Death or progression or new anticancer treatment after more than one missing assessment	4 (16.0)	4 (13.3)
Time to response (months)		
Patients with objective response		
No.	25	30
Mean (SD)	1.73 (1.14)	2.02 (1.81)
Median	1.41	1.41
Q1-Q3	0.72-2.10	0.72-2.10
Min-max	0.7-5.6	0.7-9.5

NOTE. The tumor response is based on GRS[29] criteria. IRC assessment percentages are based on the total number of patients in the PEAS. Investigator assessment percentages are based on the total number of patients in the IEAS, which is the PEAS plus two patients who were determined to have visceral disease (stage IVB) at baseline by IRC review, but which was not identified by the investigator. One cycle is 21 days per protocol. For best overall responses, PR and CR must be confirmed not <3 weeks after initial assessment of response. Stable disease must be ≥3 weeks after first dose to be considered as best overall response. Durable stable disease must be ≥23 weeks after first dose.

Abbreviations: CR, complete response; DD, denileukin diftitox; DOR, duration of response; GRS, Global Response Score; IEAS, Investigator Efficacy Analysis Set; IRC, independent review committee; KM, Kaplan-Meier; max, maximum; min, minimum; NE, not estimable; PEAS, Primary Efficacy Analysis Set; PR, partial response; Q, quartile; SD, standard deviation.

[a]95% CI is constructed using the Clopper and Pearson method.

[b]Percentages are based on the number of patients with best overall response of CR/PR.

[c]Quartiles are estimated using the KM method, and the 95% CIs are estimated using a generalized Brookmeyer and Crowley method.

historical reference study of DD.[26] Key exclusion criteria were previous DD therapy and topical steroid use within day 1 of initial therapy (except for patients with erythroderma receiving prolonged corticosteroid treatment).

Treatment Protocol

For both the lead-in study and the main study, DD-cxdl was administered intravenously over 60 (±10) minutes on 5

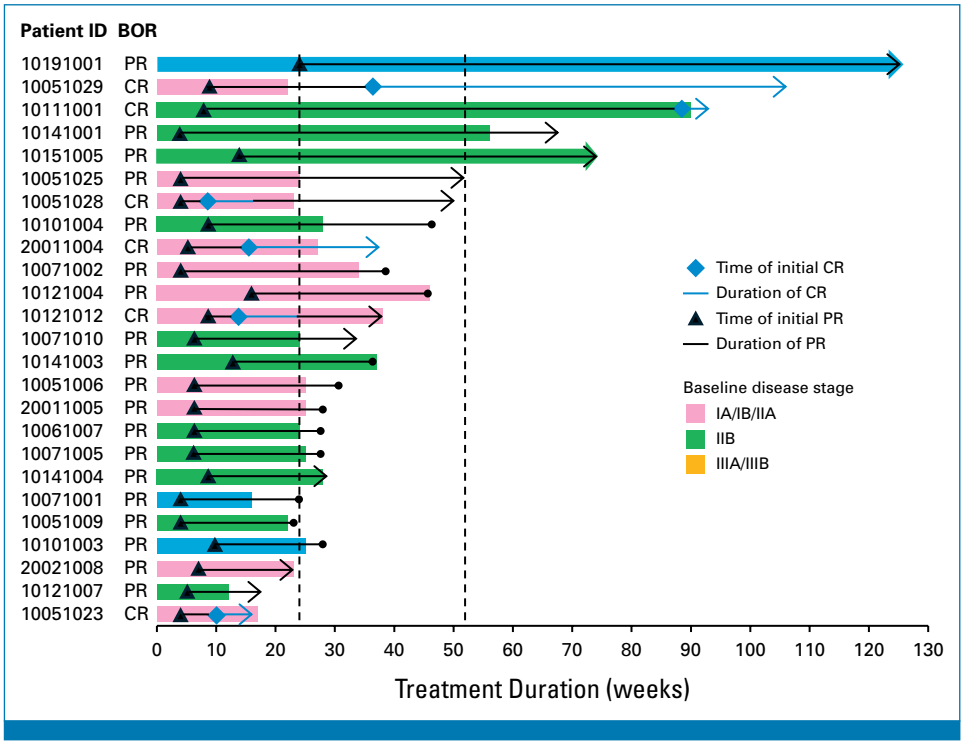

FIG 2. Swimmer plot per Global Response Score for responders—PEAS. This figure displays the best overall response, duration of treatment, and DOR for each of the 25 confirmed responders in the PEAS. Treatment is represented by solid bars that are color-coded for CTCL stage at baseline. Vertical dashed lines mark time points at 24 weeks after the first dose of study drug (eight cycles of therapy) and 52 weeks to mark 1 year on study. Blue diamonds indicate the time of initial CR, and black triangles indicate the time of initial PR. Arrowheads at the right edge of the colored (green, pink, or orange) bars indicate that treatment was ongoing at the data cutoff date; arrowheads at the right end of the lines (blue or black) indicate that DOR was censored. Black dots at the right end of the lines (black) indicate the end of response (ie, time of progressive disease, start of new anticancer therapy, or all-cause death). BOR, best overall response; CR, complete response; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; ID, patient identifier; PEAS, primary efficacy analysis set; PR, partial response.

consecutive days across 21-day cycles. In the main study, treatment continued for up to eight cycles. Patients who showed clinical benefit were allowed to receive DD-cxdl beyond eight cycles at the discretion of the treating physician. During lead-in, DD-cxdl was dosed at 6, 9, 12, and 15 μg/kg once daily for 5 consecutive days every 21 days, allocated in accordance with continual reassessment method design rules. The established MTD from the lead-in study was 12 μg/kg once daily for 5 consecutive days, with 9 μg/kg once daily for 5 days selected as the acceptable safe dose for use in the main study; this decision was based on Protocol Steering Committee input and review of efficacy and toxicity data. For all patients, premedication (acetaminophen, diphenhydramine, antiemetic agents, and hydration) was administered approximately 30 minutes before each DD-cxdl infusion in cycles 1-3 and was optional from cycle 4 onward.

Assessment Methods and Schedule

Tumor response was evaluated by an independent review committee (IRC) and per investigator. For the GRS, skin disease was assessed as change from baseline in the modified severity-weighted assessment tool (mSWAT), which measures the involved body surface area via a weighting factor applied according to skin lesion severity and type (patch, plaque, or tumor).[29] The mSWAT was to be performed by the same investigator at all time points. For blood disease assessment, quantitative flow cytometry was performed at a central laboratory. Lymph node disease was assessed by palpation and computed tomography (CT) and/or biopsy, and visceral disease was assessed using CT scan.

At screening, patients underwent blood, skin, and lymph node disease assessment (including palpation and CT scan). During treatment, patients underwent blood and skin disease assessment on day 1 of every cycle (with a 3-day window allowed). The frequency of lymph node assessment by palpation was at the investigator's judgment. Lymph node biopsy was conducted when histology would affect the primary end point analysis. CT scans of nodal and visceral disease were conducted as needed. End-of-treatment tumor assessments were performed if required for GRS determination. During follow-up, blood and skin disease assessments were performed every 4 weeks for 1 year after study

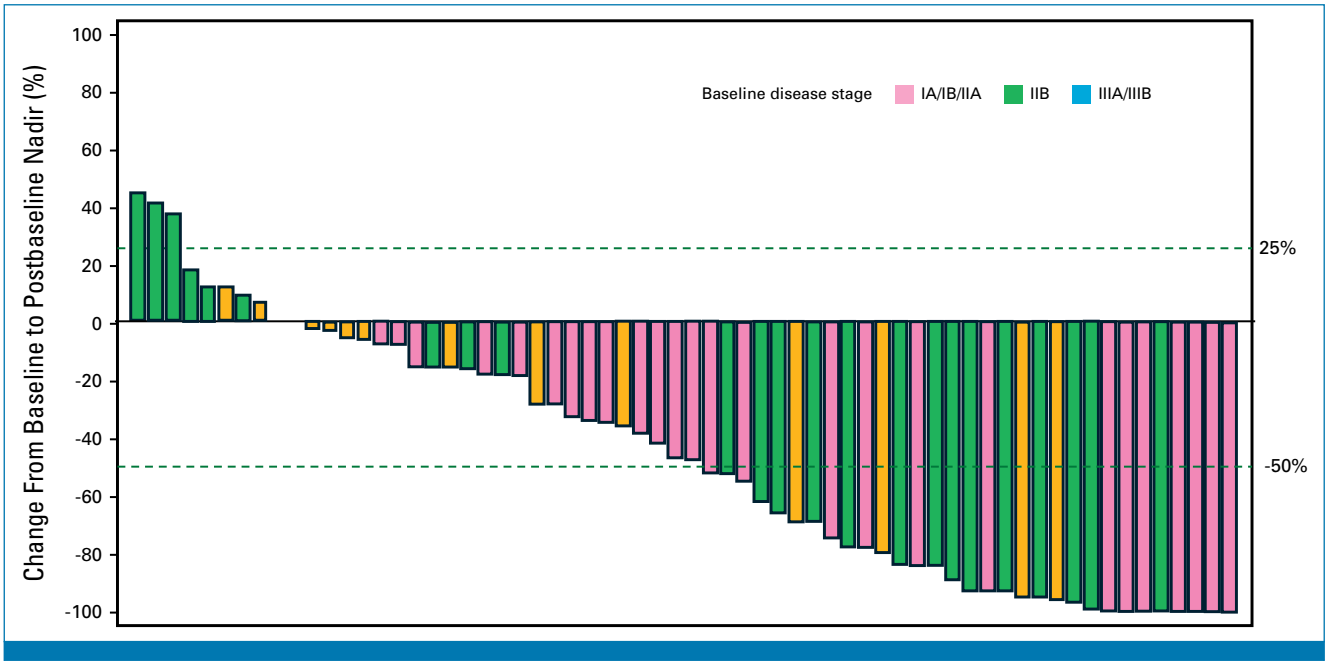

FIG 3. Waterfall plot for skin tumor burden (mSWAT score)—primary efficacy analysis set. This plot represents each patient's percent change in mSWAT score from baseline to postbaseline nadir. Of 69 patients, 64 who had baseline and ≥one postbaseline mSWAT scores were included. mSWAT, modified severity weighted assessment tool.

treatment ended, and then every 12 weeks for up to 3 years, or sooner if clinically indicated.

Safety was assessed via the regular monitoring and recording of adverse events (AEs) and serious adverse events and clinical data (ie, hematology, blood chemistry, urine values, vital signs, electrocardiograms, and physical examinations). Hematology, blood chemistry, and urinalysis samples were obtained before dispensing the study drug and were reviewed at the beginning of each treatment cycle. AE severity was assigned in accordance with Common Terminology Criteria for Adverse Events version 5.0.[30]

Statistical Analysis

The Full Analysis Set (FAS) comprised all patients with stage IA-IVA CTCL (lead-in and main study) who received ≥one dose of DD-cxdl 9 μg/kg once daily for 5 days. The primary efficacy analysis set (PEAS) comprised all patients from the FAS with stage IA-IIIB CTCL per central evaluation. The Investigator Efficacy Analysis Set (IEAS) included all patients from the FAS with stage IA-IIIB CTCL per investigator assessment. The Safety Analysis Set (SAS) comprised all patients (lead-in and main study) who received ≥one dose of DD-cxdl 9 μg/kg once daily for 5 days. The stage IA-IIIB SAS was limited to patients with stage IA-IIIB CTCL.

Efficacy analyses used IRC data as the primary analysis (PEAS) and investigator data as the secondary analysis (IEAS). Primary analyses were performed after data cutoff (December 6, 2021), defined as the latest of the following: (1) All patients had completed cycle 8 or were off treatment or (2) all patients with ≥one documented time point response of PR or better had undergone subsequent tumor assessments. Patients with missing tumor assessments were treated as nonresponders. ORR was calculated using the Clopper-Pearson method, with a two-sided, exact 95% CI. Treatment was considered clinically effective if the lower CI of the observed ORR exceeded 25%, per FDA guidance. Subgroup analyses of ORR were based on baseline disease stage and previous anticancer therapies not yet available during the original DD registration study (mogamulizumab, brentuximab vedotin, and histone deacetylase [HDAC] inhibitors). For skin tumor burden, percent change from baseline in mSWAT score was calculated for patients who had baseline and ≥one postbaseline mSWAT score. DOR, TTR, and PFS were calculated using Kaplan-Meier product-limit estimates, plotted over time, with medians and corresponding two-sided 95% CIs.

Safety analyses were performed for the SAS and stage IA-IIIB SAS, summarized using descriptive statistics (mean and standard deviation [SD], median, first and third quartiles [Q1-Q3], and minimum and maximum for continuous variables; number and percentage for categorical variables).

Statistical analyses were performed using SAS (Cary, NC) version 9.4 or higher.

RESULTS

Table 1 summarizes patient demographic and clinical baseline characteristics for the PEAS (n = 69) and FAS (n = 98). With respect to the PEAS, most patients were male (65.2%) and White (72.5%). The median age was 64.0 years (range, 28-87).

TABLE 3. Overview of TEAEs—Stage IA-IIIB SAS

Category	Stage IA-IIIB SAS (n = 69), No. (%)
Patients with any TEAEs	68 (98.6)
TEAEs grade ≥3	30 (43.5)
TEAEs grade 3, 4, 5	27 (39.1), 3 (4.3), 0
Patients with any serious TEAE[a]	26 (37.7)
Fatal serious TEAEs	0
Nonfatal serious TEAEs	26 (37.7)
Life-threatening	1 (1.4)
Requires inpatient hospitalization or prolongation of existing hospitalization	26 (37.7)
Patients with any TEAE leading to drug adjustment[a]	29 (42.0)
Study drug discontinuation	8 (11.6)
Study drug dose reduction or drug interruption	26 (37.7)
Study drug dose reduction	3 (4.3)
Study drug dose interruption	26 (37.7)

TEAE by Preferred Term Occurring in ≥10% of Patients	Any Grade, No. (%)	Grade ≥3, No. (%)
Nausea	30 (43.5)	1 (1.4)
Fatigue	22 (31.9)	0
ALT increased	19 (27.5)	6 (8.7)
Chills	19 (27.5)	1 (1.4)
Edema peripheral	19 (27.5)	1 (1.4)
AST increased	18 (26.1)	3 (4.3)
Infusion-related reaction	17 (24.6)	4 (5.8)
Headache	16 (23.2)	0
Diarrhea	13 (18.8)	0
Pruritus	13 (18.8)	4 (5.8)
Capillary leak syndrome	12 (17.4)	4 (5.8)
Pyrexia	11 (15.9)	1 (1.4)
Hypoalbuminemia	10 (14.5)	0
Decreased appetite	9 (13.0)	1 (1.4)
Dizziness	9 (13.0)	0
Vision blurred	9 (13.0)	0
Vomiting	9 (13.0)	0
Weight increased	9 (13.0)	0
Arthralgia	8 (11.6)	0
Constipation	8 (11.6)	0
Myalgia	8 (11.6)	1 (1.4)
Back pain	7 (10.1)	1 (1.4)
Insomnia	7 (10.1)	0

NOTE. MedDRA-preferred terms "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression," which are unrelated to the study drug, are excluded. Patients with two or more AEs in the same preferred term are counted only once for that preferred term with the worst CTCAE grade. AE terms were coded using MedDRA version 24.1.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, Safety Analysis Set; TEAE, treatment-emergent adverse event.

[a]Each patient may be counted in multiple categories.

Almost all patients had MF (95.7%), and 56.5% had advanced stage IIB-IIIB disease. The median number of previous anticancer therapies was 4.0, and 65.2% of patients had received ≥four previous anticancer therapies (maximum, 18). These included nonmedication treatments (photodynamic therapy [56.5%] and electron beam therapy [42.0%]), systemic retinoids (49.3%), methotrexate/pralatrexate (49.3%), HDAC inhibitors (34.8%), brentuximab vedotin (26.1%), and mogamulizumab (11.6%).

Table 2 shows primary efficacy results by both IRC and investigator assessment (Data Supplement, Table S2 shows

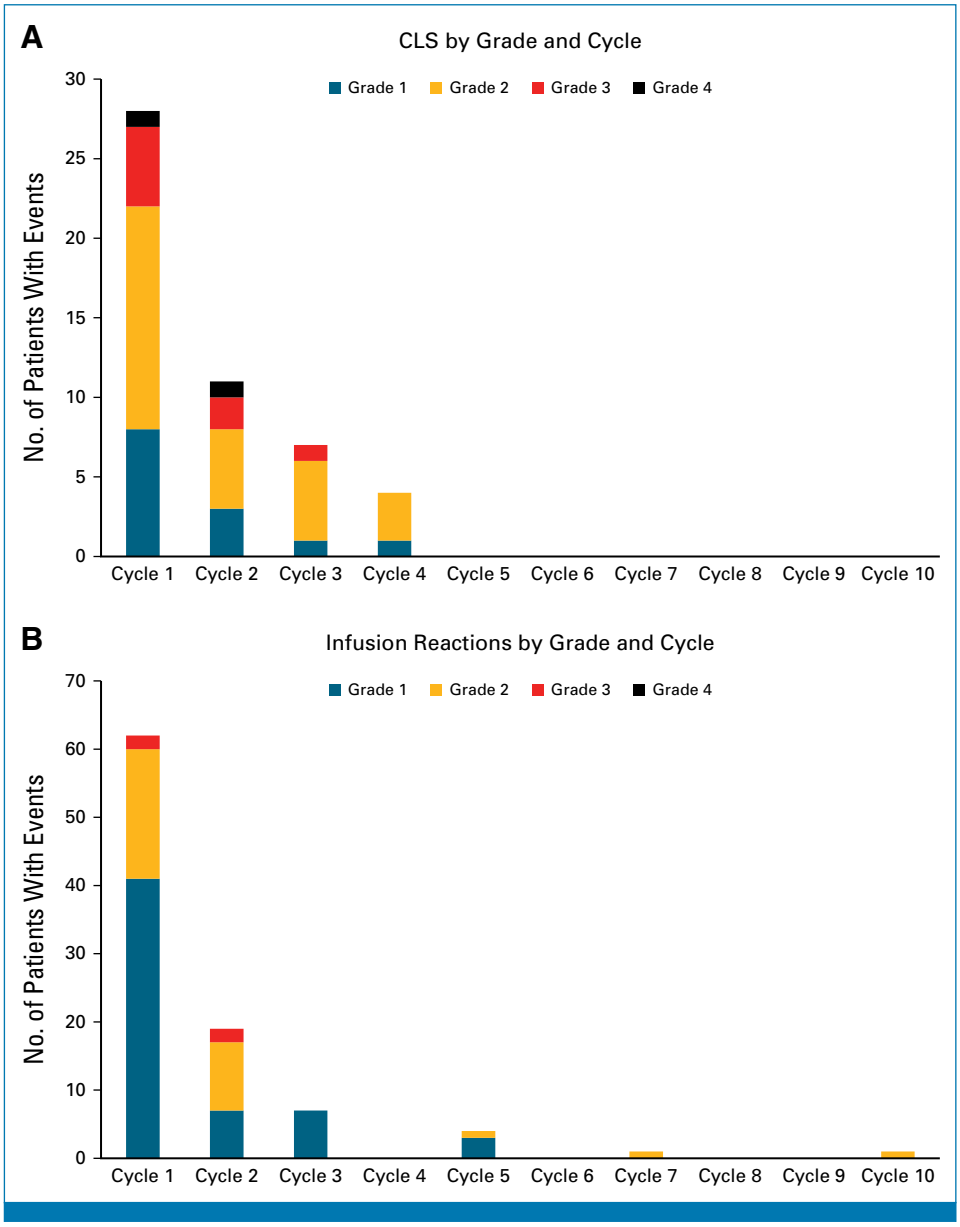

FIG 4. Occurrence over the treatment period of (A) CLS and (B) infusion reactions by grade and cycle. On the basis of CTCAE, the criteria for CLS were a preferred term of CLS and/or TEAEs in at least two of three categories assessing hypotension, edema, and hypoalbuminemia within a cycle. Instructions on dose modifications and interruptions were provided for these TEAEs. CLS, capillary leak syndrome; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse events.

FAS results, which include patients with stage IV disease). On the basis of IRC assessment of the PEAS, 25 patients achieved an objective response (ORR, 36.2% [95% CI, 25.0 to 48.7]), including six patients (8.7%) who achieved CR. The median (95% CI) TTR was short at 1.4 (0.7 to 2.1) months (Data Supplement, Fig S1). Median (95% CI) PFS was not estimable (NE [NE to NE]; Data Supplement, Fig S2). Most responders (n = 18 of 25, 72.0%) received ≥eight cycles of DD-cxdl; 15 responders (60.0%) had ongoing response after treatment discontinuation. When analyzed by CTCL stage at study entry, the ORR was 36.7% (95% CI, 19.9 to 56.1) for patients with stage IA/IB/IIA disease, 45.8% (95% CI, 25.6 to 67.2) for patients with stage IIB (T3 tumors) disease, and 20.0% (95% CI, 4.3 to 48.1) for patients with stage IIIA/IIIB (skin erythroderma) disease (see Data Supplement, Table S3, which also shows stage IV disease results).

Among patients who previously received HDAC inhibitors, brentuximab vedotin, or mogamulizumab (combined n = 34), the ORR was 35.3% (95% CI, 19.7 to 53.5; Data Supplement, Table S4). Overall, relatively minor differences in the clinical benefit rate (CR + PR + durable stable disease) were seen between patients who received versus did not receive one of these targeted therapies. However, patient

numbers were small, and the study was not powered to detect differences between subgroups.

Figure 2 shows a swimmer plot summarizing best overall response, treatment duration, and DOR for all confirmed PEAS responders. The median (range) observed DOR was 6.47 (3.0+ to 23.5+) months, and the median (95% CI) DOR by Kaplan-Meier analysis was 8.9 (5.0 to NE) months (Data Supplement, Fig S3). Thirteen (52.0%) and five (20%) patients showed an observed DOR of ≥6 and ≥12 months, respectively.

Figure 3 shows a waterfall plot summarizing maximum change from baseline in skin tumor burden for PEAS patients (n = 64) with mSWAT scores obtained at baseline and ≥one time postbaseline. Most patients (54 of 64, 84.4%) showed decreased skin tumor burden, with 31 (48.4%) showing a maximum decrease of ≥50% and eight (12.5%) showing 100% clearance of skin disease.

Exposure and Safety

The Data Supplement (Table S5) shows treatment disposition data for the PEAS and FAS. In the PEAS, the mean (SD) number of cumulative cycles received was 7.0 (6.3), with a median of 6.0 cycles (range, 1-42). Nineteen patients (27.5%) received ≥nine cumulative treatment cycles. As of data cutoff, two (2.9%) patients had ongoing treatment, and the remainder had discontinued, including 12 (17.4%) who completed the planned eight-cycle regimen and 55 (79.7%) for other reasons (eg, PD [n = 28, 40.6%], patient choice [n = 13, 18.8%], or AEs [n = 7, 10.1%]).

Nearly all stage IA-IIIB SAS patients (68 of 69; 98.6%) had ≥one TEAE, most commonly nausea (43.5%); fatigue (31.9%); and increased ALT, chills, and peripheral edema (27.5% each; Table 3). These events were generally grade 1 or 2. TEAE incidence was higher in cycles 1 and 2 (5.3 and 2.2 events per patient, respectively), then decreased, and remained low and stable for the remainder of therapy (0.7 events per patient in cycle 8). Three patients (3.1%) had TEAEs leading to dose reduction. Most drug dose interruptions happened in cycles 1 and 2, and patients were able to continue therapy after restarting at full dose. See the Data Supplement (Table S6) for equivalent FAS safety results, including patients with stage IV disease.

The Data Supplement (Table S7) summarizes TEAEs of special interest for both safety sets. Sixty-four patients (92.8%) in the stage IA-IIIB SAS had ≥one TEAE of special interest; most were grade 1 or 2 (65.6%). Most common were infusion reaction (73.9%), hypersensitivity (68.1%), hepatotoxicity (36.2%), and capillary leak syndrome (CLS; 20.3% [grade ≥3, 5.8%]). Nineteen patients (27.5%) had serious TEAEs of special interest, leading to study drug discontinuation in five (7.2%; of which three [4.3%] were due to CLS), dose reduction in three (4.3%), and drug interruption in 18 (26.1%). There was no evidence of cumulative toxicity because of TEAEs of special interest (Fig 4).

DISCUSSION

This study confirms the efficacy and tolerability of DD-cxdl in heavily pretreated patients with R/R CTCL, with an ORR of 36.2% and a median DOR of 8.9 months. Early response was seen at a median of 1.4 months (cycles 1 or 2). This ORR is similar to that obtained in other studies of DD-cxdl[22,23] and historical DD.[26] In the phase III trial of historical DD, patients with stage IA-IIIB CTCL treated at the same dose as the current study (9 μg/kg once daily for 5 days; n = 45) achieved an ORR of 37.8% and a median DOR of 9.1 months.[26] In addition, data from the current study indicate the potential for a sustained clinical benefit with prolonged response: overall response was maintained after treatment discontinuation in 60.0% of IRC responders and observed DOR was maintained for ≥12 months in 20.0%.

Clinically meaningful responses were observed in patients with different skin manifestations. Although 56.5% of patients in the PEAS had advanced CTCL (stages IIB-IIIB), 84.4% showed a decreased skin tumor burden with DD-cxdl treatment, with 12.5% experiencing 100% skin lesion clearance. This was further exemplified by a robust ORR in patients with T3 skin tumors (stage IIB) of 45.8% (95% CI, 25.6 to 67.2) and in patients with erythroderma (stage IIIA/IIIB) of 20.0% (95% CI, 4.3 to 48.1). Similarly, the placebo-controlled trial of historical DD showed activity in patients with stage IA-IIIB disease, with durable response and disease stage at baseline shown in multivariate analysis to have no significant effect on ORR.[26] These findings are promising, given that patients in the current study were heavily pretreated with a median of four previous therapies, including common therapeutic mainstays and newer targeted therapies including mogamulizumab, brentuximab vedotin, and HDAC inhibitors. Patients previously treated with these newer targeted therapies demonstrated a 35.3% ORR.

The observed safety profile with DD-cxdl was consistent with results observed for patients with CTCL who participated in previous studies assessing DD-cxdl[22,23] and historical DD.[26] Although TEAEs of special interest occurred in 27.5% of the PEAS, including CLS in 20.3%, there was no evidence of cumulative toxicity, and incidence decreased and remained low and stable for the remainder of therapy. In addition, TEAEs of special interest led to treatment discontinuation in only 7.2% of patients (4.3% because of CLS), indicating a tolerable treatment profile.

In conclusion, DD-cxdl's unique mechanism of action targeting the IL-2 receptor differentiates it from other currently available, targeted treatments for CTCL. It addresses an unmet medical need for safe, effective treatments that offer the potential of durable response to patients with heavily pretreated, R/R CTCL.[28] Future studies evaluating the antitumor activity of the combination of DD-cxdl with other active systemic agents are planned.

AFFILIATIONS

[1]Yale University School of Medicine, New Haven, CT
[2]Departments of Dermatology & Medicine, Stanford Cancer Center, Stanford, CA
[3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia
[4]University of Pittsburgh Medical Center-Presbyterian Shadyside, Pittsburgh, PA
[5]City of Hope Medical Center, Duarte, CA
[6]Department of Dermatology, University of South Florida, Tampa, FL
[7]Eli Lilly and Company, Indianapolis, IN
[8]Dana-Faber Cancer Institute, Boston, MA
[9]Rush University Medical Center, Chicago, IL
[10]Department of Medicine, Northwestern University, Chicago, IL
[11]Epworth HealthCare, Melbourne, Australia
[12]Department of Clinical Pathology, University of Melbourne, Parkville, Australia
[13]Columbia University Medical Center, New York, NY
[14]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ
[15]H. Lee Moffit Cancer Center and Research Institute, Inc., Tampa, FL
[16]Winship Cancer Institute of Emory University, Atlanta, GA
[17]University of Florida Health Shands Hospital, Gainesville, FL
[18]Hospital Español Auxilio Mutuo/Auxilio Mutuo Cancer Center, San Juan, PR
[19]University of Arkansas for Medical Sciences, Little Rock, AR
[20]Eisai Inc., Nutley, NJ
[21]Citius Pharmaceuticals, Cranford, NJ
[22]Department of Dermatology, The University of Texas—MD Anderson Cancer Center, Houston, TX

CORRESPONDING AUTHOR

Francine M. Foss, MD; e-mail: francine.foss@yale.edu.

PRIOR PRESENTATION

Presented at 64th American Society of Hematology (ASH) Annual Meeting and Exposition, New Orleans, LA, December 10-13, 2022.

SUPPORT

Supported by Dr Reddy's Laboratories. In September 2021, Citius Pharmaceutical Inc acquired denileukin diftitox-cxdl (formerly E7777), along with all commercialization and intellectual property rights.

CLINICAL TRIAL INFORMATION

NCT01871727

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-01549.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-01549.

AUTHOR CONTRIBUTIONS

Conception and design: Francine M. Foss, H. Miles Prince, Nam Hoang Dang, Chean Eng Ooi, Dongyuan Xing, Preeti Singh, Madeleine Duvic
Financial support: Francine M. Foss, Myron Czuczman
Administrative support: Francine M. Foss, Myron Czuczman
Provision of study materials or patients: Francine M. Foss, Youn H. Kim, Oleg E. Akilov, Christiane Querfeld, David C. Fisher, Timothy M. Kuzel, Costas K. Yannakou, Tatyana Feldman, Lubomir Sokol, Pamela Blair Allen, Fernando Cabanillas, Chean Eng Ooi
Collection and assembly of data: Francine M. Foss, Youn H. Kim, H. Miles Prince, Christiane Querfeld, Lucia Seminario-Vidal, David C. Fisher, Timothy M. Kuzel, Costas K. Yannakou, Larisa J. Geskin, Tatyana Feldman, Lubomir Sokol, Pamela Blair Allen, Fernando Cabanillas, Henry K. Wong, Chean Eng Ooi, Dongyuan Xing, Nicholas Sauter, Preeti Singh, Myron Czuczman
Data analysis and interpretation: Francine M. Foss, Youn H. Kim, H. Miles Prince, Oleg E. Akilov, Christiane Querfeld, Lucia Seminario-Vidal, David C. Fisher, Costas K. Yannakou, Larisa J. Geskin, Lubomir Sokol, Pamela Blair Allen, Nam Hoang Dang, Chean Eng Ooi, Dongyuan Xing, Nicholas Sauter, Preeti Singh, Myron Czuczman
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

Medical writing support was provided by Caitlin Rothermel, MA, MPH, and Naseem Bazargan, MPH, of MedLitera.

REFERENCES

1. Porkert S, Valencak J: Cutaneous lymphomas—Fast facts about an orphan disease—A short review. memo—Mag Eur Med Oncol 16:10-16, 2023
2. Thandra KC, Barsouk A, Saginala K, et al: Epidemiology of non-Hodgkin's lymphoma. Med Sci (Basel) 9:5, 2021
3. Dobos G, Pohrt A, Ram-Wolff C, et al: Epidemiology of cutaneous T-cell lymphomas: A systematic review and meta-analysis of 16,953 patients. Cancers (Basel) 12:2921, 2020
4. Cai ZR, Chen ML, Weinstock MA, et al: Incidence trends of primary cutaneous T-cell lymphoma in the US from 2000 to 2018: A SEER population data analysis. JAMA Oncol 8:1690-1692, 2022
5. Kempf W, Mitteldorf C: Cutaneous T-cell lymphomas—An update 2021. Hematol Oncol 39:46-51, 2021 (suppl 1)
6. National Comprehensive Cancer Network (NCCN): NCCN Clinical Practice Guidelines in Oncology. Primary cutaneous lymphomas. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
7. Olsen E, Vonderheid E, Pimpinelli N, et al: Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: A proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 110:1713-1722, 2007
8. Mourad A, Gniadecki R: Overall survival in mycosis fungoides: A systematic review and meta-analysis. J Invest Dermatol 140:495-497 e5, 2020
9. Brunner PM, Jonak C, Knobler R: Recent advances in understanding and managing cutaneous T-cell lymphomas. F1000Res 9:F1000 Faculty Rev-331, 2020
10. Hristov AC, Tejasvi T, A Wilcox R: Cutaneous T-cell lymphomas: 2021 update on diagnosis, risk-stratification, and management. Am J Hematol 96:1313-1328, 2021
11. Whittaker SJ, Marsden JR, Spittle M, et al: Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 149:1095-1107, 2003
12. Scarisbrick JJ, Bagot M, Ortiz-Romero PL: The changing therapeutic landscape, burden of disease, and unmet needs in patients with cutaneous T-cell lymphoma. Br J Haematol 192:683-696, 2021
13. Willemze R, Hodak E, Zinzani PL, et al: Primary cutaneous lymphomas: ESMO clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29:iv30-iv40, 2018 (suppl 4)
14. Assaf C, Waser N, Bagot M, et al: Contemporary treatment patterns and response in relapsed/refractory cutaneous T-cell lymphoma (CTCL) across five European countries. Cancers (Basel) 14:145, 2021
15. Eklund JW, Kuzel TM: Denileukin diftitox: A concise clinical review. Expert Rev Anticancer Ther 5:33-38, 2005
16. Olsen E, Duvic M, Frankel A, et al: Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 19:376-388, 2001

17. vanderSpek JC, Mindell JA, Finkelstein A, et al: Structure/function analysis of the transmembrane domain of DAB389-interleukin-2, an interleukin-2 receptor-targeted fusion toxin. The amphipathic helical region of the transmembrane domain is essential for the efficient delivery of the catalytic domain to the cytosol of target cells. J Biol Chem 268:12077-12082, 1993
18. Bachanova V, Cooley S, Defor TE, et al: Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein. Blood 123:3855-3863, 2014
19. Rasku MA, Clem AL, Telang S, et al: Transient T cell depletion causes regression of melanoma metastases. J Transl Med 6:12, 2008
20. ONTAK (denileukin diftitox) [prescribing information]. Ridgefield Park, NJ, Eisai Medical Research Inc, 2020
21. U.S. Food and Drug Administration: Denileukin diftitox—Product approval information—Licensing action. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1999/denser020599L.htm
22. Ohmachi K, Ando K, Ogura M, et al: E7777 in Japanese patients with relapsed/refractory peripheral and cutaneous T-cell lymphoma: A phase I study. Cancer Sci 109:794-802, 2018
23. Kawai H, Ando K, Maruyama D, et al: Phase II study of E7777 in Japanese patients with relapsed/refractory peripheral and cutaneous T-cell lymphoma. Cancer Sci 112:2426-2435, 2021
24. Eisai launches Remitoro for PTCL and CTCL in Japan. The Pharma Letter. https://www.thepharmaletter.com/article/eisai-launches-remitoro-for-ptcl-and-ctcl-in-japan
25. LYMPHIR™ (denileukin diftitox-cxdl) [prescribing information]. Cranford, NJ, Citius Pharmaceuticals, Inc, 2024
26. Prince HM, Duvic M, Martin A, et al: Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol 28:1870-1877, 2010
27. Wheeler GM, Mander AP, Bedding A, et al: How to design a dose-finding study using the continual reassessment method. BMC Med Res Methodol 19:18, 2019
28. Citius Pharmaceuticals, Inc: Biologics license application for E7777. Submitted to the U.S. FDA October 2022. Data on file
29. Olsen EA, Whittaker S, Kim YH, et al: Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: A consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 29: 2598-2607, 2011
30. U.S. Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Denileukin Diftitox-Cxdl, an Improved Purity Formulation of Denileukin Diftitox, in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Francine M. Foss
Consulting or Advisory Role: Seagen, Eisai, Acrotech Biopharma, Secura Bio
Speakers' Bureau: Seagen
Research Funding: Kyowa Hakko Kirin (Inst), Daiichi Sankyo (Inst), Eisai (Inst), Astex Pharmaceuticals (Inst)

Youn H. Kim
Consulting or Advisory Role: Kyowa Hakko Kirin, Innate Pharma, Corvus Pharmaceuticals, CRISPR Therapeutics, DAAN Biotherapeutics
Research Funding: Kyowa Hakko Kirin (Inst), Innate Pharma (Inst), CRISPR Therapeutics (Inst), DAAN Biotherapeutics (Inst), Pfizer (Inst)
Patents, Royalties, Other Intellectual Property: Royalty for Chapters in UpToDate
Travel, Accommodations, Expenses: Innate Pharma

H. Miles Prince
Honoraria: Bristol Myers Squibb/Celgene, Mundipharma, Mallinckrodt/Therakos
Speakers' Bureau: Mallinckrodt/Therakos
Research Funding: AbbVie (Inst)

Oleg E. Akilov
Speakers' Bureau: Kyowa Kirin International, Ortho Dermatologics, Helsinn Therapeutics
Research Funding: Mallinckrodt/Therakos

Christiane Querfeld
Honoraria: Kyowa Kirin International, Helsinn Therapeutics
Consulting or Advisory Role: Kyowa Kirin International, Helsinn Therapeutics, Citius Pharmaceuticals
Research Funding: Helsinn Therapeutics, Kyowa Kirin International

Lucia Seminario Vidal
Employment: Lilly
Stock and Other Ownership Interests: Lilly
Travel, Accommodations, Expenses: Lilly

David C. Fisher
Consulting or Advisory Role: Genentech, Gilead Sciences, Kyowa Hakko Kirin, Verastem

Timothy M. Kuzel
Honoraria: Merck, Cardinal Health, Seagen, CVS, Kyowa Kirin International, Bristol Myers Squibb Foundation, EnGeneIC, Fidia Farmaceutici S. p. A, Pfizer, Sun Pharma, Janssen Research & Development
Consulting or Advisory Role: enGene
Speakers' Bureau: Genomic Health
Patents, Royalties, Other Intellectual Property: Up to Date Section editor on cutaneous lymphomas
Other Relationship: Sun Pharma, Janssen Research & Development

Larisa J. Geskin
Consulting or Advisory Role: Helsinn Therapeutics, SciTech Development LLC, Kyowa Kirin
Research Funding: Mallinckrodt, Kyowa Kirin, Stratpharma, Incyte, Merck, Innate Pharma, Soligenix

Tatyana Feldman
Stock and Other Ownership Interests: OM Pharmaceutical Industries, Genomic Testing Cooperative
Honoraria: ADC Therapeutics, AstraZeneca, Epizyme, Genmab, SeaGen, Pharmacyclics, Takeda, Bristol Myers Squibb
Consulting or Advisory Role: ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Epizyme, Genmab, Seagen, Pharmacyclics
Speakers' Bureau: Takeda, Seagen, Genmab
Research Funding: Bristol Myers Squibb (Inst), ADC Therapeutics (Inst), AstraZeneca (Inst), Corvus Pharmaceuticals (Inst), Daiichi (Inst), Genmab, Kymera (Inst), Merck (Inst), Seagen (Inst), Tessa Therapeutics (Inst), Trillium Therapeutics (Inst), Alexion Pharmaceuticals (Inst), Portola Pharmaceuticals (Inst)

Lubomir Sokol
Consulting or Advisory Role: Kyowa Kirin International, CRISPR Therapeutics, Citius Pharmaceuticals
Travel, Accommodations, Expenses: AstraZeneca, Acrotech Biopharma

Pamela Blair Allen
Honoraria: Kyowa Kirin International, Seattle Genetics/Astellas
Consulting or Advisory Role: Seattle Genetics/Astellas, Daichii Sankyo, Kyowa Kirin International, BostonGene

Fernando Cabanillas
Research Funding: Merck (Inst), AbbVie/Genentech (Inst)

Henry K. Wong
Stock and Other Ownership Interests: CRISPR Therapeutics

Chean Eng Ooi
Employment: Eisai

Dongyuan Xing
Employment: Eisai

Nicholas Sauter
Employment: Eisai
Travel, Accommodations, Expenses: Eisai

Preeti Singh
Employment: Citius Pharmaceuticals, Dr Reddy's Lab Inc
Leadership: Citius Pharmaceuticals
Stock and Other Ownership Interests: Citius Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Hold a patent for E7777. Regulatory T-cell depletion by IL-2–based immunotherapy in

combination with anti–PD-1 led to significantly increased antitumor activity and overall survival in solid tumor models

Myron Czuczman
Employment: Citius Pharmaceuticals
Stock and Other Ownership Interests: Citius Pharmaceuticals

No other potential conflicts of interest were reported.