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ORIGINAL REPORT

Phase III Placebo-Controlled Trial of Denileukin Diftitox for Patients With Cutaneous T-Cell Lymphoma

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ABSTRACT

Purpose
This phase III, placebo-controlled, randomized trial was designed to investigate efficacy and safety of two doses of denileukin diftitox (DD; DAB_{389}–interleukin-2 [IL-2]), a recombinant fusion protein targeting IL-2 receptor–expressing malignant T lymphocytes, in patients with stage IA to III, CD25 assay–positive cutaneous T-cell lymphoma (CTCL), including the mycosis fungoides and Sézary syndrome forms of the disease, who had received up to three prior therapies. The primary end point was overall response rate (ORR).

Patients and Methods
Patients (N = 144) with biopsy-confirmed, CD25 assay–positive CTCL were randomly assigned to DD 9 μg/kg/d (n = 45), DD 18 μg/kg/d (n = 55), or placebo infusions (n = 44), administered for 5 consecutive days every 3 weeks for up to eight cycles. Patients were monitored for drug efficacy, clinical benefit, and safety of DD.

Results
ORR was 44% for all participants treated with DD (n = 100; 10% complete response [CR] and 34% partial response [PR]) compared with 15.9% for placebo-treated patients (2% CR and 13.6% PR). ORR was higher in the 18 μg/kg/d group versus the 9 μg/kg/d group (49.1% *v* 37.8%, respectively), and both doses were significantly superior to placebo. Progression-free survival (PFS) was significantly longer (median, > 2 years) for both DD doses compared with placebo (median, 124 days; $P < .001$). Rates of moderately severe and severe adverse events (AEs) were slightly higher in the DD groups, whereas moderate and mild AEs were similar to placebo. No statistical differences were observed for drug-related serious AEs.

Conclusion
DD had a significant and durable effect on ORR and PFS with an acceptable safety profile in patients with early- and late-stage CTCL.

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCLs) are extranodal non-Hodgkin's lymphomas distinguished by skin lesions infiltrated with malignant $CD4^+$ or $CD8^+$ T lymphocytes.[1,2] CTCL comprises a spectrum of cutaneous lymphomas, including the most common forms mycosis fungoides and Sézary syndrome.[3]

Current CTCL therapies include cytotoxic chemotherapy, corticosteroids, photopheresis, interferon, retinoids/rexinoids (ie, bexarotene), and histone deacetylase inhibitors.[4-10] Despite responses to first-line therapies, most patients ultimately experience relapse,[11-20] with survival rates declining for patients with late-stage disease,[14,20] illustrating the need for new therapies.

Denileukin diftitox (DD; DAB_{389}–interleukin-2 [IL-2], ONTAK; Eisai, Woodcliff Lake, NJ) is a genetically engineered fusion protein combining the cytotoxic and membrane-translocating domains of the diphtheria toxin with the full-length sequence of human IL-2. The cytocidal action of diphtheria toxin targets cells expressing the high-affinity IL-2 receptor, inhibiting protein synthesis and promoting cell death. The human IL-2 receptor consists of three subunits, α (CD25), β (CD122), and γ (CD132), and depending on the level of expression of each subunit, affinity of the receptor for IL-2 can be defined as low, intermediate, or high.[21] DD binds to, is internalized by, and most efficiently kills cells that express the intermediate- or high-affinity IL-2 receptor.[22-25] An earlier trial presented evidence for the efficacy and safety of DD in patients with CTCL.[26]

Study L4389-11, presented here, was a multicenter, randomized, international trial designed to evaluate the efficacy and clinical benefit of two dose levels of DD versus placebo. With 144 patients, to our knowledge, it represents the largest prospective study to date for patients with CTCL and the only placebo-controlled study of systemic therapy completed in this patient population. A companion phase III trial, to be reported elsewhere, was conducted to assess DD efficacy in patients with CD25 assay–negative CTCL, in patients with CD25 assay–positive CTCL previously receiving placebo on study L4389-11, and in a third group of patients to evaluate the benefit of retreatment in patients who had previously responded.[27]

PATIENTS AND METHODS

Study Population

Patients with stages 1A to III disease with histopathologic confirmation of CTCL[28] and who had ≤ three previous therapies and CD25 assay–positive expression (defined as detectable CD25 on ≥ 20% of T cells in biopsied skin lesions by immunohistochemistry) were enrolled. Immunohistochemistry was performed by a central laboratory on frozen tissue samples. Protocol approval was obtained from institutional and/or country review boards. All enrolled patients signed written informed consent.

Key entry requirements were age ≥ 18 years, CTCL evaluable for response (skin and blood), Eastern Cooperative Oncology Group performance status of 0 or 1, ≤ three prior therapies (regardless of number of courses or repeat treatment), only one prior systemic CTCL regimen, and no prior treatment with DD. Key exclusion criteria were involvement of the bone marrow (determined in patients with > 20% circulating abnormal lymphocytes), liver, or spleen; biopsy-confirmed lymph node status ≥ LN3 (defined as a large cluster of cells in a dermatopathic node indicating lymphoma involvement); and the presence of high-grade or large-cell, poorly differentiated tumors. Patient outcomes were recorded until the event of progressive disease (PD), relapse, or initiation of new anticancer therapy, leading to study discontinuation.

Treatment

Patients were randomly assigned in a double-blind fashion to one of the following three treatment arms: placebo, DD 9 μg/kg/d, or DD 18 μg/kg/d (Fig 1). Random assignment was stratified by disease stage, according to early- (≤ IIA) or advanced-stage (≥ IIB) CTCL. DD and placebo were administered as a daily 30- to 60-minute intravenous (IV) infusion on days 1 through 5 of each course. Courses were repeated every 21 days for up to eight courses over a total treatment duration of approximately 6 months. Premedication with acetaminophen and an antihistamine was required 30 to 60 minutes before each infusion, and these medications were allowed during and after the dosing period, as needed. Pretreatment with corticosteroids was prohibited.

Patients who developed grade 2 or 3 toxicities were allowed up to 7 days of dose interruptions, and patients experiencing dose-limiting toxicities could delay the next course of treatment by up to 14 days. Dose reductions were not allowed. For relief of CTCL symptoms, patient rescue medications (oral hydroxyzine, topical emollients, and bath additives) were permitted.

Assessment of Efficacy

Responses were adjudicated by a data end point review committee, a team of two clinicians (one dermatologist and one oncologist) who performed blinded, independent, parallel reviews of all individual tumor burden assessments, photography, and, when indicated, radiologic films, to adjudicate the clinical outcome for each patient. A third reviewer served as referee to review and adjudicate any discrepancies between the two primary reviewers.

Tumor burden was assessed at baseline, on day 1 of courses 2 through 8, and during follow-up by measurement of skin lesions using a Severity-Weighted Assessment Index, in which the sizes/areas of skin lesions were weighted for severity using a multiplier of 1 for patch lesions, 2 for plaque lesions, and 4 for tumors.[29] Patient response was assessed at each study visit based on percent changes in tumor burden relative to baseline. All lesions were

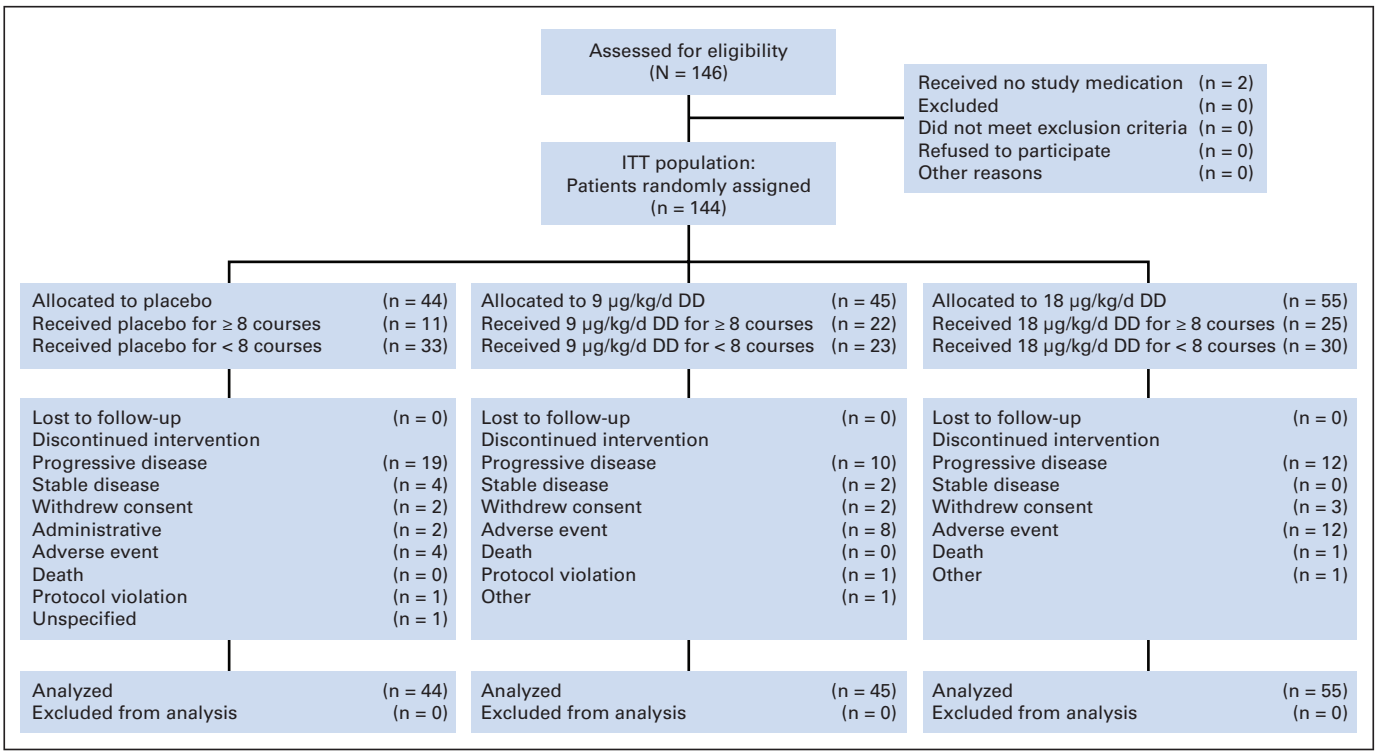

Fig 1. Disposition of patients who were screened (n = 146) and randomly assigned (n = 144) to receive placebo, denileukin diftitox (DD) 9 μg/kg/d, or DD 18 μg/kg/d. ITT, intent-to-treat.

Table 1. Demographics and Baseline Clinical Characteristics of Randomly Assigned Patients

Characteristic	Placebo (n = 44)		DD 9 μg/kg/d (n = 45)		DD 18 μg/kg/d (n = 55)		All Patients (N = 144)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Skin involvement								
Mycosis fungoides	37	84.1	39	86.7	47	85.5	123	85.4
Sézary syndrome	4	9.1	2	4.4	3	5.5	9	6.3
Other	3	6.8	4	8.9	5	9.1	12	8.3
Age, years								
Median	59.0		58.0		61.0		59.0	
Range	23-80		32-82		32-84		23-84	
< 65 years	26	59.1	32	71.1	37	67.3	95	66.0
≥ 65 years	18	40.9	13	28.9	18	32.7	49	34.0
Sex								
Female	23	52.3	19	42.2	23	41.8	65	45.1
Male	21	47.7	26	57.8	32	58.2	79	54.9
Race								
White	34	77.3	40	88.9	50	90.9	124	86.1
Black	8	18.2	5	11.1	5	9.1	18	12.5
Hispanic	1	2.3	0	0.0	0	0.0	1	0.7
Other	1	2.3	0	0.0	0	0.0	1	0.7
Disease stage								
≤ IIA	30	68.2	29	64.4	38	69.1	97	67.4
≥ IIB	14	31.8	16	35.6	17	30.9	47	32.6
No. of prior anticancer therapies								
None	4	9.1	8	17.8	8	14.5	20	13.9
1	10	22.7	13	28.9	13	23.6	36	25.0
2	16	36.4	13	28.9	18	32.7	47	32.6
3	12	27.3	8	17.8	13	23.6	33	22.9
> 3	2	4.5	3	6.7	3	5.5	8	5.6

Abbreviation: DD, denileukin diftitox.

evaluated in participants with lesions that were more than 10% of total body-surface area; patients with skin lesions ≤ 10% of body-surface area had up to five representative skin lesions evaluated. Patients who had both skin lesions and ≥ 20% abnormal peripheral lymphocytes at baseline were assessed by average percent change in affected areas and in abnormal peripheral lymphocytes. Documented responses for all end points had to be confirmed at three consecutive visits (ie, maintained for ≥ 6 weeks after the initial documentation).

Primary end point. Overall response rate (ORR) was defined as the percentage of patients with complete response (CR; no clinical evidence of disease based on tumor burden assessment and histopathology of skin with biopsy-confirmed absence of atypical cells), clinical CR (CCR; same as CR but either histopathology indicated the presence of atypical cells or histopathologic confirmation was unavailable), or partial response (PR; ≥ 50% reduction in tumor burden relative to baseline). PD was defined as ≥ 25% increase in tumor burden relative to baseline or the appearance of a new skin tumor, new ≥ LN3 lymph nodes, or visceral disease. Stable disease was defined as insufficient change in tumor burden relative to baseline to qualify for the preceding categories.[30]

Secondary end points. Progression-free survival (PFS) was defined as the time from the first day of treatment to first observation of tumor progression or death from any cause up to 30 days after last dose of study drug. Patients who did not experience progression were censored at the last day of efficacy assessment. Duration of response (DR) was defined as time from the date a response was first documented until date of relapse, new cancer treatment, or last observation. Time to response (TTR) was defined as time from day 1 of course 1 to first confirmed response. Time to treatment failure (TTF) was defined as time from day 1 of treatment to date of PD or discontinuation for toxicity.

Supportive end points. Supportive end points to assess clinical benefit of DD treatment included Patient Global Skin Assessment, Patient's Pruritus Assessment, Physician's Global CTCL Severity Assessment, and Physician's Erythroderma Severity Assessment.

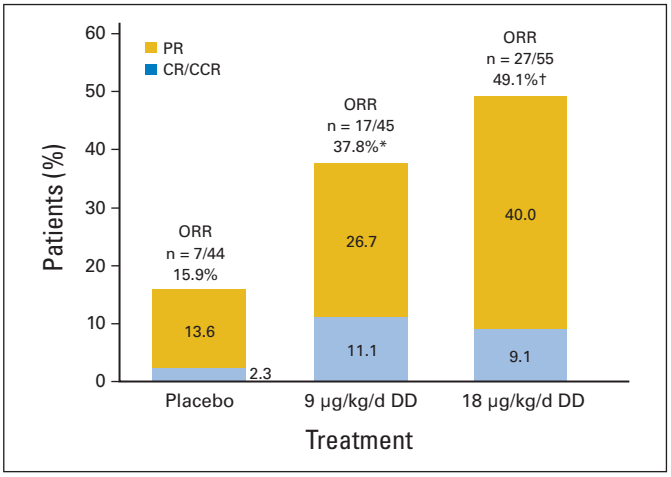

Fig 2. Overall response rate (ORR) in 144 patients who were randomly assigned to receive placebo, denileukin diftitox (DD) 9 μg/kg/d, or DD 18 μg/kg/d. ORRs (values above bars) were the combination of complete response (CR), clinical complete response (CCR), and partial response (PR) (values within bars). (*) $P = .029$ *v* placebo. (†) $P = .0015$ *v* placebo.

Assessment of Safety

Safety monitoring included physical examination, assessment of adverse events (AEs), vital signs, and clinical laboratory values (serum chemistry, hematology, and urinalysis) at all visits and at any time during the study. Severity of AEs was graded as mild (grade 1), moderate (grade 2), moderately severe (grade 3), or severe (grade 4). Serious AEs (SAEs) were those that required medical intervention to prevent death or resulted in life-threatening AE drug experience, hospitalization, persistent or significant disability, or death.

Specific syndrome-related AEs, infusion reactions, and capillary leak/vascular leak syndrome (CLS) were defined by sets of related events. Infusion reaction was defined as symptoms occurring within 24 hours of infusion and resolving within 48 hours of the last infusion in that course, including hypersensitivity reactions and flu-like symptoms. CLS comprised a set of AEs, including hypotension, edema, and a serum albumin level of less than 3.0 g/dL, and was defined as the occurrence of at least two of these three symptoms, which could occur individually at any time during a course of treatment.

Statistical Analysis

The efficacy analysis included the intent-to-treat population (all randomly assigned patients). Treatment group testing involved a step-down multiple comparison procedure to test pairwise hypotheses, with a two-sided $\alpha = .05$. The conditional logistic regression model[31,32] stratified patients by random assignment allocation ratios, treatment categories, and disease stage. A significant result at the two-sided $\alpha = .05$ level for DD 18 μg/kg/d versus placebo was followed by a similar analysis of DD 9 μg/kg/d versus placebo, as well as a comparison of the combined DD groups versus placebo. Two-sided exact 95% CIs were determined for the observed tumor response rates in individual and combined-dose groups.

Secondary end points (PFS, DR, TTR, and TTF) were analyzed using the log-rank test, Kaplan-Meier method, and estimated Cox regression hazard ratios. Supportive end points were measured as the percentage of patients who achieved clinically significant improvements in assessment scores for each treatment group, compared with placebo, using the logistic regression exact method. Concordance of supportive end points with tumor response was correlated using the κ statistic.

AEs were classified and organized by MedDRA (version 6; http://www.meddramsso.com/) into organ class, preferred term, severity, and study drug relationship. Mean, standard deviation, and range were statistical analyses used to summarize laboratory data, including vital signs, by treatment group.

Table 2. Primary and Secondary End Points in Randomly Assigned Patients

End Point	Placebo (n = 44)	DD 9 μg/kg/d (n = 45)	DD 18 μg/kg/d (n = 55)	Both DD Arms (n = 100)
Primary end points				
Overall response				
ORR, %	15.9	37.8	49.1	44.0
No. of responders	7	17	27	44
Primary analysis *P**†	—	.0297	.0015	.0026
Best response				
CR or CCR				
No. of patients	1	5	5	10
%	2.3	11.1	9.1	10.0
PR				
No. of patients	6	12	22	34
%	13.6	26.7	40.0	34.0
SD				
No. of patients	14	16	19	35
%	31.8	35.6	34.5	35.0
PD				
No. of patients	23	12	9	21
%	52.3	26.7	16.4	21.0
Secondary end points				
PFS				
Median, days (KM)	124	794	> 971*	794
Log-rank *P*, DD *v* placebo	—	.0024	< .001	< .001
HR	—	0.42	0.27	0.32
DR				
Median, days (KM)	81	277	220	236
Log-rank *P*, DD *v* placebo	—	.0128	.0038	.0016
TTR				
Median, days (KM)	> 204‡	120	92	96
Log-rank *P*, DD *v* placebo	—	.0152	< .001	.0011
HR	—	2.87	3.81	3.43
TTF				
Median, days (KM)	93	155	169	155
Log-rank *P*, DD *v* placebo	—	.0047	.0089	.0022
HR	—	0.47	0.51	0.50

Abbreviations: DD, denileukin diftitox; ORR, overall response rate; CR, complete response; CCR, clinical complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; KM, Kaplan-Meier method; HR, hazard ratio; DR, duration of response; TTR, time to response; TTF, time to treatment failure.

*Stratified logistic regression model and a step-down multiple-comparison procedure.

†Effect of cutaneous T-cell lymphoma stage, $P = .8039$.

‡Last data point; median not reached.

RESULTS

Disposition and Demographics

There were no statistical differences in the demographic characteristics of patients randomly assigned to either dose group compared with placebo (Table 1). Two thirds of patients (overall and within each dose group) had early-stage (≤ IIA) CTCL. Histologic diagnosis was characterized as mycosis fungoides (85.4%), Sézary syndrome (6.3%), or other (8.3%). Number of prior therapies is listed in Table 1.

Patients were treated according to the randomized regimen (Fig 1), with a median of six treatment courses (61.8% of patients received ≥ five courses). Forty-seven percent of patients treated with DD and 25% of patients treated with placebo completed ≥ eight treatment courses, with a trend for a higher frequency of early termination in the placebo group (75.0%) versus both the DD 18 μg/kg/d group (54.5%; $P = .0673$) and the DD 9 μg/kg/d group (51.1%; $P = .0683$). Dose adjustments (delay or suspension) occurred in 17% of all patients (7% on placebo and 20% on DD).

Frequency of prior therapies (approximately 90% of patients were previously treated and experienced progression) had no impact on response to DD. Prior therapies included phototherapy (48%), interferon alfa (20%), electron beam radiotherapy (24%), systemic cytotoxic chemotherapy (26%), topical chemotherapy (25%), and other therapies (30%).

Efficacy

Primary end point analysis. ORR, based on the data end point review committee assessment, showed a statistically significant superiority for both doses of DD versus placebo (Fig 2). The ORR for the DD 18 μg/kg/d group was 49.1% (9.1% CCR/CR and 40.0% PR) compared with 15.9% for placebo (2.3% CR/CCR and 13.6% PR; $P = .0015$). For the DD 9 μg/kg/d group, the ORR was 37.8% (11.1% CCR/CR and 26.7% PR; $P = .0297$ *v* placebo). PD was recorded in 52.3% of placebo patients but in only 21% of all DD-treated patients (Table 2).

The treatment courses in which initial responses were recorded in all DD responders (n = 44) were as follows: course 2, 25% (n = 11); course 3, 29.5% (n = 13); course 4, 9.1% (n = 4); course 5, 13.6% (n = 6); course 6, 6.8% (n = 3); course 7, 0%; and course 8+, 15.9% (n = 7). Multivariate analysis showed that no baseline variable had a significant effect on response (disease stage, $P = .94$; sex, $P = .47$; race, $P = .21$; age, $P = .71$; number of prior CTCL therapies, $P = .55$).

Secondary end points. Outcomes for all secondary end points were also statistically superior for DD-treated patients versus patients who received placebo (Table 2). PFS was significantly longer for patients treated with DD versus placebo (Fig 3). Estimated median PFS time was at least 971 days for the DD 18 μg/kg/d group, 794 days for the DD 9 μg/kg/d group, and only 124 days for placebo patients. A Cox regression analysis, stratified for random assignment ratio and adjusted for disease stage, predicted a hazard ratio of 0.27 for DD 18 μg/kg/d versus placebo ($P < .001$), a 73% reduction in risk of disease progression or death in this group, and a hazard ratio of 0.42 for DD 9 μg/kg/d versus placebo ($P = .02$; Table 2).

DR in both DD groups (median, 236 days) was significantly better ($P = .0016$) compared with placebo (median, 81 days; Appendix Fig A1, online only). TTR for DD-treated patients (96 days for both DD groups) was significantly shorter than with placebo (Appendix Fig A2, online only). Estimated median TTF for the DD 18 and 9 μg/kg/d dose groups was 169 and 155 days, respectively, compared with 93 days in the placebo group (Appendix Fig A3, online only).

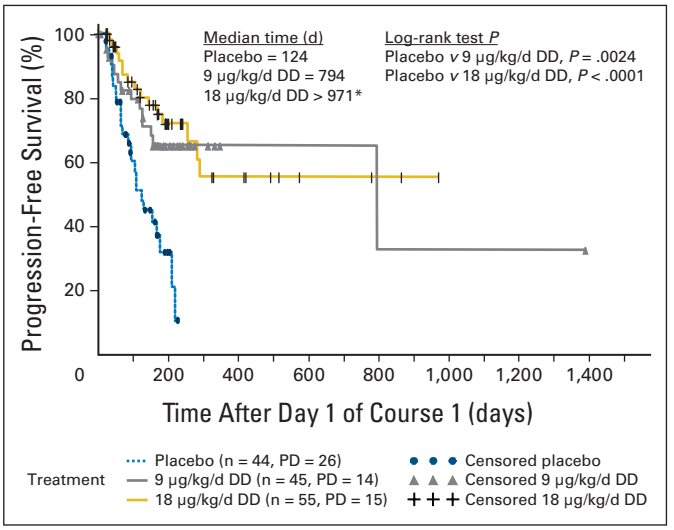

Fig 3. Kaplan-Meier estimates of progression-free survival (PFS; N = 144). PFS was defined as time from day 1 of course one to first observation of progressive disease (PD) or death from any cause. Blue line with circles indicates placebo group with censoring events (n = 44; PD, n = 26). Gray line with triangles indicates denileukin diftitox (DD) 9 μg/kg/d group with censoring events (n = 45; PD, n = 14). Gold line with crosses indicates DD 18 μg/kg/d group with censoring events (n = 55; PD, n = 15). (*) Final data point shown. Median was not reached.

Tumor burden. Median time for a ≥ 25% reduction in tumor burden was 92 days for the placebo group and statistically significantly shorter (43 days) for both of the DD groups.

Safety

This study provided, for the first time to our knowledge, the opportunity to compare AEs in DD treatment arms with AEs of a matched placebo cohort from the same population, offering invaluable insight into the true incidence of DD-related toxicity and the AEs that are related to the underlying disease or unrelated to treatment. The percentages of patients reporting AEs and SAEs were higher for DD than for placebo (Table 3). The percentage of patients reporting moderate and mild AEs was similar in both DD groups. A summary of AEs reported by ≥ 10% of study patients (regardless of relationship to treatment) can be found in Appendix Table A2 (online only). The incidence of serious AEs (SAEs) was relatively low in all treatment arms (Table 3). Statistical comparison of all SAEs (regardless of relationship to study drug) indicated that only sepsis was significantly more frequent in the placebo group than in the DD groups (6.8% *v* 0%, respectively; $P < .05$). Sepsis was considered unrelated to study therapy.

CLS as a distinct AE (defined as the occurrence of two or three of the following events: hypoalbuminemia, edema, and hypotension at

Table 3. Overview of AEs

AE	Placebo (n = 44)		DD 9 μg/kg/d (n = 45)		DD 18 μg/kg/d (n = 55)		Both DD Arms (n = 100)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any AE	40	90.9	44	97.8	53	96.4	97	97.0
Study drug–related AE	26	59.1	41	91.1	52	94.5	93	93.0
SAE	9	20.5	16	35.6	16	29.1	32	32.0
Study drug–related SAE	2	4.5	12	26.7	13	23.6	25	25.0
Study drug–related capillary leak syndrome (grade 3/4)	0	0.0	2	4.4	2	3.6	4	4.0
Discontinuation as a result of study drug–related AE	3	6.8	6	13.3	11	20.0	17	17.0
Moderately severe study drug–related AEs (≥ 5% incidence)								
Abdominal pain	0	0.0	3	6.7	0	0.0	3	3.0
Nausea	0	0.0	3	6.7	7	12.7	10	10.0
Vomiting	0	0.0	1	2.2	3	5.5	4	4.0
Asthenia	0	0.0	2	4.4	4	7.3	6	6.0
Fatigue	2	4.5	3	6.7	9	16.4	12	12.0
Pyrexia	0	0.0	6	13.3	5	9.1	11	11.0
Rigors	0	0.0	6	13.3	6	10.9	12	12.0
Anorexia	0	0.0	0	0.0	3	5.5	3	3.0
Arthralgia	1	2.3	3	6.7	3	5.5	6	6.0
Back pain	0	0.0	2	4.4	3	5.5	5	5.0
Myalgia	0	0.0	3	6.7	4	7.3	7	7.0
Dyspnea	1	2.3	2	4.4	3	5.5	5	5.0
Hypotension	0	0.0	1	2.2	3	5.5	4	4.0
Flushing	0	0.0	0	0.0	3	5.5	3	3.0
Severe study drug–related AEs (≥ 3% incidence)								
Dehydration	0	0.0	2	4.4	0	0.0	2	2.0
Capillary leak syndrome (grade 4)	0	0.0	0	0.0	2	3.6	2	2.0

Abbreviations: DD, denileukin diftitox; AE, adverse event; SAE, serious adverse event.

any time during therapy) was reported in 10 patients receiving DD (10%). Of the patients with CLS, two had moderately severe CLS (2%), and two were classified as severe (2%; Table 3).

Analysis of AEs and SAEs by treatment course revealed a consistent pattern; the frequencies of all DD-related AEs were highest during the initial two or three treatment courses and declined to placebo levels by course 4 (Figs 4A and 4B). A similar pattern of reduced frequency in subsequent courses was seen for specific syndrome-related AEs of infusion reactions and CLS.

No apparent difference was observed in the rate of infections. Repeated courses of DD were not associated with immunosuppression, as manifested by no differences in fungal, viral, or bacterial infection frequency. Absolute lymphocyte counts decreased in 22% of patients on DD during the first treatment course and then rebounded and remained at normal levels after course 2. For clinical chemistry AEs, a similar pattern of transient changes in early courses with recovery and stabilization by course 3 or 4 was observed. Continued treatment did not cause worsening of laboratory parameters and was not associated with liver or renal toxicity.

DISCUSSION

This study confirms and further validates the efficacy, clinical benefit, and safety of DD in patients with CD25 assay–positive, stage IA to III CTCL. A prior study had shown positive responses to DD in a population that had a larger proportion of late-stage patients (up to stage IV) who were more heavily pretreated.[26] The results in this larger, stratified, placebo-controlled trial show a highly significant difference in efficacy, as assessed by ORR, for both DD dose groups and for the combined DD group versus placebo. A multivariate analysis of the primary end point indicated no significant effects of stage, sex, race, age, or number of prior CTCL therapies on the primary end point. A consistent observation across all end points (with exception of DR) was a superior outcome for the DD 18 μg/kg/d group.

Hazard ratios for secondary time-to-event end points (combined DD or individual DD dose *v* placebo) indicated that DD provided clinical benefit to patients with CTCL across all clinical benefit assessments. Of particular note was the large prolongation (> 2 years) of PFS in DD-treated patients compared with the placebo group (0.3 years). Similar beneficial and significant differences were recorded for DR, TTR, and TTF. Taken together, all the secondary parameters addressing clinical benefit support the advantageous effects on response rates and tumor burden reduction afforded by DD treatment.

For the first time to our knowledge, this study documents that responses can be observed in patients receiving placebo, probably reflecting the waxing and waning of skin lesions that have been described in CTCL patients. Analysis of placebo responses indicated significantly shorter PFS and lesser benefits as measured by secondary and supporting end points addressing clinical benefit. Importantly, these differences in magnitude and duration of response were confirmed in a parallel study, which included a large number of the placebo patients who crossed over to active treatment.[27]

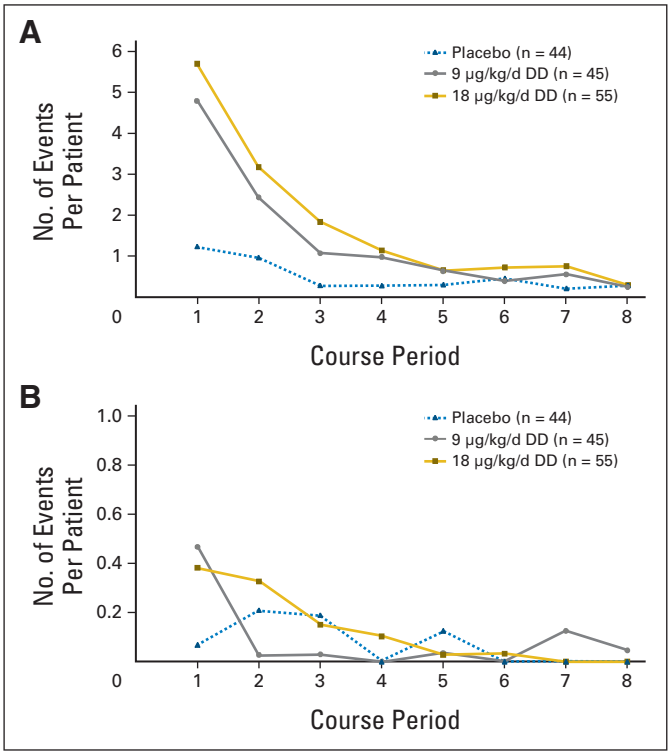

Fig 4. (A) Study drug–related adverse events by treatment course and (B) serious adverse events by treatment course. Blue line indicates placebo group (n = 44). Gray line indicates denileukin diftitox (DD) 9 μg/kg/d group (n = 45). Gold line indicates DD 18 μg/kg/d group (n = 55).

An acceptable safety profile for DD was demonstrated in this study. For appropriate clinical decisions on treatment continuation, it is important to note that the frequencies of all AEs, including CLS, were highest during the initial two treatment courses, declining to placebo levels in later courses, whereas 45% of responses to treatment were confirmed in courses 4 to 8 or later. It should be noted that strategies to further reduce reactions to DD infusion in early cycles, such as dexamethasone pretreatment, were not allowed in this trial.

The absence of a dose response for safety suggests that the DD 18 μg/kg/d dose may improve the response rate without increasing toxicity. The 18 μg/kg/d dose provides more benefit, such as a higher ORR and statistically significant improvements in several supportive end points.

DD received full US Food and Drug Administration approval for the treatment of CD25 assay–positive CTCL on October 15, 2008. The outcomes of this study clearly support the conclusion that DD is both safe and efficacious for the therapy of patients with CTCL at different stages of the disease and with different levels of pretreatment. DD may represent an important treatment option for many patients with these challenging diseases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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