analyses: Clark level (II-III and unknown or IV-V), thickness (≤0.75 mm or 0.76-1 mm), tumor-infiltrating lymphocytes (present or absent), and mitoses (present or absent). For lesions in which an individual characteristic was not reported, the characteristic was recorded as unknown. Only patients with known mitotic rate data were included in the regression analyses (n = 698).[5] Histologic subtype was not included in the previous analysis, thus providing the basis for this reanalysis.

This study was approved, with a waiver for patient informed consent, by the Institutional Review Board of the University of Pennsylvania.

Results | In our new prognostic model inclusive of histologic subtype, univariable analysis identified nodular melanoma (OR, 3.80) and acral lentiginous melanoma (ALM) (OR, 8.17) (P = .01 for both) as factors significantly associated with SLN positivity. By multivariable logistic regression analysis, ALM remained a factor significantly associated with SLN positivity (OR, 16.02; P = .004), as did increased Clark level (OR, 3.04; P = .02) and mitotic rate of 1 mm^2 or more (OR, 6.04; P = .01). Sentinel lymph node positivity was found in 2 of 10 patients (20%) with ALM, 5 of 48 patients (10%) with nodular melanoma, 14 of 534 patients (3%) with superficial spreading melanoma, and none of 37 patients with lentigo maligna melanoma. Of the patients in the group with ALM, 9 of 10 (90%) were non-Hispanic white and 1 of 10 (10%) was Hispanic white. Nine of the 10 ALM lesions were found on the foot and 1 ALM lesion was found on the hand. Thickness (OR, 2.22; P = .09) and nodular melanoma (OR, 2.48; P = .09) showed a trend toward, but did not reach, statistical significance in our model (**Table**).

Discussion | The reanalysis found that the histologic subtype of ALM as well as mitoses and Clark level IV-V were independent predictors of SLN positivity. This finding is limited, however, by the relatively small number of patients (n = 10) with ALM in the cohort on which the reanalysis was done. The finding of ALM as a predictor of SLN metastasis should be further confirmed in other studies. Although the rate of SLN positivity was low for the study cohort of patients with thin melanomas (3.7%), a subset of patients can be identified with appreciable rates of nodal metastasis, who can be stratified for risk by the Clark level, mitotic rate, and histologic subtype of their melanoma. Further study of these factors can help guide clinical decision-making in patients with thin melanomas.

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Efficacy and Safety of APO866 in Patients With Refractory or Relapsed Cutaneous T-Cell Lymphoma: A Phase 2 Clinical Trial

For cutaneous T-cell lymphoma (CTCL),[1] there is need for new treatment options. APO866 is an injectable molecule that induces cell death by inhibiting the biosynthesis of NAD^+ (oxidized nicotinamide adenine dinucleotide), which is essential for cell survival.[2-4] Previous studies have shown in vitro and in vivo that lymphocytes and hematologic cancer cells are very sensitive to APO866, which induced cell death at low concentration in various human tumor cells, including lymphomas.[5]

Methods | This open-label, single-arm, multicenter, phase 2 clinical trial took place from February 2007 to January 2011. We analyzed the efficacy (measured by objective response rates using the Tumor Burden Index [TBI][6] for cutaneous disease and imaging for extracutaneous disease), safety, and tolerability (using descriptive statistics) of APO866 in relapsed or refractory CTCL. APO866 (provided by Apoxis SA and later by Topotarget A/S) was administered every 28 days for a total of 3 cycles by continuous intravenous infusion via pump at 0.126 $mg/m^2/h$ over the course of 96 hours. The study was approved by the respective national and regional ethics commit-

Table 1. Patient Characteristics, Outcomes, and AEs

Patient No./ Sex/Age, y	Diagnosis	Stage	Outcome, Week 8/ Week 16	Completed Treatment	AEs[a]
1/M/70s	MF	IIB	PD/NR[b]	No	None, unrelated, or grade <3
2/F/60s	Sézary syndrome	IVA	SD/SD	Yes	None, unrelated, or grade <3
3/F/40s	MF	IIB	PD/NR[b]	No	None, unrelated, or grade <3
4/F/60s	MF	IVA	SD/SD	Yes	None, unrelated, or grade <3
5/F/30s	Anaplastic large-cell lymphoma CD30$^+$	IVA	PD/NR[b]	No	Intermittent fever (grade 3)
6/M/40s	MF	IVA	PR/SD	Yes	None, unrelated, or grade <3
7/M/30s	Poikilodermic MF	IIA	SD/SD	Yes	None, unrelated, or grade <3
8/M/10s	MF	IVA	NR[c]	No	None, unrelated, or grade <3
9/F/70s	MF	IIA	NR[c]	No	Lymphopenia (grade 4), thrombopenia (grade 3), anemia (grade 3)
10/M/60s	Sézary syndrome	IVA	NR[d]	No	Lymphopenia (grade 3), spondylitis-staphylococcus septicemia (grade 4, n=2), rhabdomyolysis (grade 2, SAE)
11/F/50s	MF	IIB	SD/PR	Yes	None, unrelated, or grade <3
12/F/80s	Nonepidermotropic cutaneous T-cell lymphoma CD30$^-$	IB	PD/NR[b]	No	Lymphopenia (grade 4)
13/M/60s	Sézary syndrome	IVA	NR[c]	No	Thrombocytopenia (grade 3)
14/M/80s	MF	IVA	PD/NR[b]	No	None, unrelated, or grade <3

Abbreviations: AE, adverse event; MF, mycosis fungoides; NR, not reported; PD, progressive disease; PR, partial response; SD, stable disease; SAE, serious adverse event.

[a] Only grade 3 to 5 AEs judged related to the study drug or SAEs judged related to study drug are listed.

[b] Outcome at 16 weeks not evaluable because patient did not complete study.

[c] Not evaluable due to withdrawal of the patient.

[d] Not evaluable due to early termination caused by AE.

Table 2. CTCL Response to Treatment With APO866[a]

Visit Week	Patients, No.[b]	CCR	PR		SD		PD	
		No. (%)	No. (%)	90% CI	No. (%)	90% CI	No. (%)	90% CI
8	6	0	1 (16.7)[c]	0.9-58.2	4 (66.7)	27.1-93.7	1 (16.7)	0.9-58.2
16	12	0	1 (8.3)[d]	0.4-33.9	6 (50.0)	24.5-75.5	5 (41.7)	18.1-68.5

Abbreviations: CCR, complete clinical response; CTCL, cutaneous T-cell lymphomas; ITT, intention-to-treat; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Primary end point, overall response in the final ITT analysis.

[b] Two patients withdrew consent and were evaluated as missing.

[c] This patient had stable disease (stage IVA) at week 16.

[d] This patient had stable disease (stage IIB) at week 8.

tees and conducted according Good Clinical Practice guidelines (NCT00431912), and all participants provided their written informed consent.

All the patients had a histologically confirmed diagnosis of CTCL, including mycosis fungoides and Sézary syndrome,[1] ranging from stage IB to stage IVB disease according to TNM staging and had relapsed or refractory disease or were intolerant to 2 or more prior systemic therapies.

The primary efficacy end point was defined as the proportion of patients who achieved complete response (CR) or partial response (PR, defined as ≥50% TBI reduction from baseline) assessed at week 16.[6] The statistical design of the trial was an extension of the Simon optimal design and based on a trinomial model. The study was conducted according to the optimal 2-stage design with trilevel end points (CR + PR, stable disease [SD], and progressive disease [PD]). A prespecified efficacy evaluation was planned after recruitment of the first 11 patients. In case of the presence of 2 or more responders (PR or CR), the study would continue up to the recruitment of a total of 25 patients. These calculations assumed type I and type II error rates of 10%. We report the results of the prespecified efficacy analysis after the recruitment of the first 14 patients.

Results | Fourteen patients, 7 women and 7 men (age range, 19-83 years), were enrolled in the study and were part of the intention-to-treat analysis. One patient was classified as having stage IB CTCL; 2 and 3 patients were classified as having stage IIA and IIB disease, respectively; and 8 patients had stage IVA CTCL (**Table 1**). Five patients were considered treated per protocol (PP) (n = 5). The PP population included all patients who completed all 3 treatment cycles and had no major protocol violations. Nine of the 14 patients terminated the trial before completion of the 3 treatment cycles and were excluded from the PP analysis owing to consent withdrawal (n = 2), early disease progression (n = 5), or development of adverse events (AEs) (n = 2). There was no major protocol violation.

The overall response to therapy including cutaneous and extracutaneous disease is summarized in **Table 2.** At week 16, 1 patient (1 of 12) had achieved PR; 6 of 12 had SD; and 5 of 12 had PD. No participant achieved CR. In the PP-treated group, 1 of 5 had PR, and 4 of 5 had SD. A total of 141 AEs were reported, of which 77 were judged to be drug related. Most patients (86%; n = 12) experienced mild to moderate AEs. In general, AEs affected rapidly regenerative tissues such as blood cells and gastrointestinal tissue. Hematologic changes included anemia, thrombocytopenia, and lymphopenia. A total

of 18 serious AEs occurred, 7 of which were judged to be drug related. These included pyrexia, lymphopenia (n = 2), spondylitis, staphylococcal sepsis, rhabdomyolysis, and thrombocytopenia. Four deaths were reported but not considered study-drug related.

Discussion | In previous studies, APO866 induced cell death at low concentration in human hematologic malignancy cells, including lymphomas.[5] No resistance mechanisms are known. In the present study, APO866 showed a reasonable toxic effect in CTCL. Severe lymphocytopenia and thrombocytopenia were observed, and the other AEs were mild to moderate. However, the drug was not powerful enough, and the study was stopped early after the prespecified interim analysis owing to lack of drug efficacy. For these reasons, we do not see a justification for further development of APO866 in CTCL. However, owing to its mode of action with immunosuppression and insulin-mimicking effects, APO866 might play a role the treatment of other conditions.

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OBSERVATION

Posaconazole Substitution for Voriconazole-Associated Phototoxic Effects

Voriconazole is used for long-term prophylaxis or treatment of fungal infections. Voriconazole-induced phototoxic effects and photocarcinogenesis is an independent risk factor for squamous cell carcinoma (SCC) development in organ transplant recipients.[1] An alternative for patients at risk for cutaneous cancer has not been well studied. We describe a patient with voriconazole-induced photocarcinogenesis whose symptoms and tumor count improved after substitution with posaconazole.

Report of a Case | A light-skinned woman in her 70s had been receiving voriconazole and low-dose corticosteroids since 2008 for suppression of chronic *Exophiala dermatitidis* meningitis. The infection might have been due to tainted epidural corticosteroid administration. She had no history of hematologic cancer, solid organ transplantation, or other immunosuppressed state. History of skin cancer included melanoma in situ treated in 2002.

Several months after initiating voriconazole therapy, she developed widespread actinic damage and phototoxic effects (**Figure 1**A). Over 21 months (from March 2014 through December 2015), the patient had 348 actinic keratoses (AKs)