SGX301 as a Rapid, Safe and Effective Treatment for Early Stage CTCL

Authors:

- **Brian Poligone, MD, PhD,** Director, Rochester Skin Lymphoma Medical Group, Fairport, NY, USA and Lead Enroller of the HPN-CTCL-01 study
- **Henry Wong, MD, PhD,** Professor and Chair, Dermatology Cancer Clinic at Winthrop P. Rockefeller Cancer Institute
- **Aaron Mangold, MD,** Assistant Professor of Dermatology, Mayo Clinic
- **Jennifer DeSimone, MD,** Director, Cutaneous Lymphoma, Schar Cancer Institute
- **Lucia Seminario-Vidal, MD, PhD,** Assistant Professor USF Health Morsani Center for Advanced Healthcare
- **Ellen Kim, MD,** Professor of Dermatology, Hospital of the University of Pennsylvania and Lead Investigator of the HPN-CTCL-01 study

I. Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare cancer as listed in the National Organization for Rare Disorders (NORD): Rare Diseases Database[1], with a prevalence of approximately 20,000 patients in the US. CTCL is an incurable cancer that is slowly progressive and requires chronic maintenance therapies.[2] The skin develops red and scaly patches and plaques that are created by infiltrating lymphocytes. Progression involves expansion of skin patches/plaques/erythema, ulcerative nodules and tumors, spread to the lymph nodes and the blood, and rarely into other organs.[3] Currently, there is unmet medical need as patients continually transition between various treatment modalities to manage serious and accumulating risk of side effects, including various skin cancers and skin damage.[4–8] Indeed, the side effect profiles of currently available agents limit their long-term utility.[9,10] All therapies for CTCL are either approved as second-line therapies due to their potential toxicities, or are used off-label with none of them having been characterized in randomized, placebo-controlled clinical trials. Therefore, well-characterized therapies that have a rapid onset of action and minimal long term/accumulative side effects profile are crucial to the treatment of CTCL.

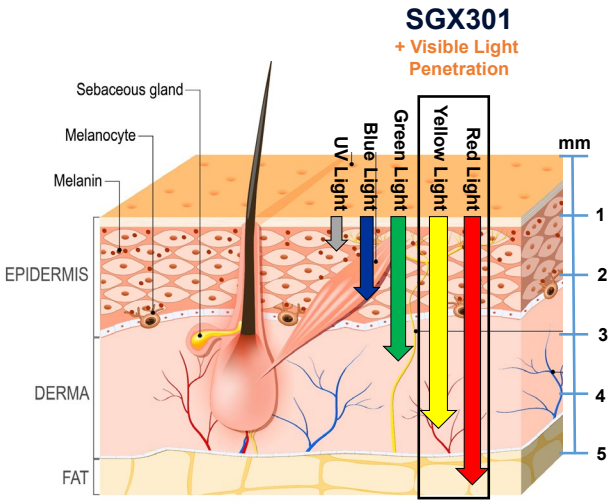
a. SGX301 Mechanism of Action

SGX301 (synthetic hypericin) has been shown to selectively absorb into T-cells, and particularly malignant T-cells [11,24,25], yielding a targeted response profile for CTCL. Moreover, apoptosis is primarily driven by the formation of reactive oxygen species after light application, yielding a 2-step paradigm to enhance tumor targeting selectivity. As a consequence, SGX301 is expected to have enhanced safety relative to other, more indiscriminately targeted treatment paradigms.

Activation of SGX301 utilizes visible light in the red-yellow spectrum. The use of visible (versus ultraviolet) light significantly reduces the risk of skin damage and skin cancers. Moreover, lack of dependence on blue light spectrum also minimizes the potential for ocular damage caused by blue light.[12]

The use of red-yellow visible wavelengths also enables deep penetration of the activating light, potentially allowing treatment of thicker and/or deeper lesions in CTCL (**Figure 1**).

Figure 1: Light Penetration of Skin Layers as a Function of Wavelength.



II. SGX301 Is Effective in CTCL

In a large, randomized, placebo-controlled study of CTCL that enrolled 169 subjects over 4 years (i.e., Study HPN-CTCL-01; **Figure 2**), biweekly topical treatment with SGX301 yielded statistically significant improvement, yielding a 16% response rate (p=0.04) after only 6 weeks of treatment (**Table 1**).

While 16% of patients achieved a treatment response (i.e., at least 50% reduction in cumulative lesion score across 3 index lesions), more broadly the average change in cumulative CAILS score was 24% across all subjects, indicating that many patients had some improvement. This incremental improvement also informs physician and patient decision making and is further supported by the results after 12 weeks of treatment (assessed at week 16 – see **Figure 2**), where the treatment response rate increased to 40% (p<0.0001; **Table 1**), and where the average reduction in lesion score was 37% over baseline.

This rapid response profile is extremely meaningful for this population. Treating physicians would normally wait months in clinical practice to evaluate what kind of response they were observing to form a conclusion with respect to the risk-benefit ratio of continuing therapy versus transitioning to another treatment modality. Having earlier time points that are significant provides the physician with more power to make these decisions earlier in the treatment process.

The response rate in this study was rigorously defined in a placebo-controlled setting, which is very rare in the CTCL context. This enhances the confidence of patients and physicians in assessing the utility of the treatment. Unfortunately, due to the lack of rigor in assessing other treatment modalities, comparative statements regarding the efficacy of other treatment modalities is very difficult. Nevertheless, there is some clinical trial data available for mechlorethamine and bexarotene gel.

No prior therapeutics have demonstrated efficacy with a similar or better response rate (i.e., 16%) over such a short interval of time (i.e., 6 weeks treatment) in a placebo-controlled clinical trial. Mechlorethamine gel (non-inferiority trial between pharmacy prepared and centrally prepared formulations of mechlorethamine) did not show responses until at least 8 weeks of continuous once daily treatment and took almost 13 weeks of continuous treatment to reach a 16% response rate.[14] Bexarotene

gel also did not achieve 16% until at least day 60 (9 weeks of continuous treatment).[15] Even when treating for months, physicians do not expect to see maximal responses. Indeed, it has become standard practice to treat patients with mechlorethamine, bexarotene gel or other therapies until disease progression rather than for a fixed schedule of time.

Figure 2: HPN-CTCL-01 Study Design

Patients were randomized 2:1 to receive 0.25% SGX301 ointment or a placebo-matched ointment. All patients received visible light treatments, starting at 5 J/cm^2 that could be systematically increased by 1 J/cm^2 at each biweekly visit until light erythema was observed (maximum light dose was 12 J/cm^2). Ointment was applied 18-24 hours prior to light therapy and ointment treated lesions were kept covered (clothing or bandages) until the light therapy was completed at the physician's office. Treatment in each cycle was undertaken twice a week for 6 weeks, and then the lesion scores were again assessed after a 2-week rest period to allow the light induced erythema to fade. Cycles 1 (blinded) and 2 (cross-over design with all subjects receiving SGX301) were both initiated at the 5 J/cm^2 light dose level. Cycle 3 was optional and considered more of a compassionate use type of cycle, where patients could treat up to all of their lesions, and the light dose was continued from the maximum value obtained in Cycle 1 and / or 2.

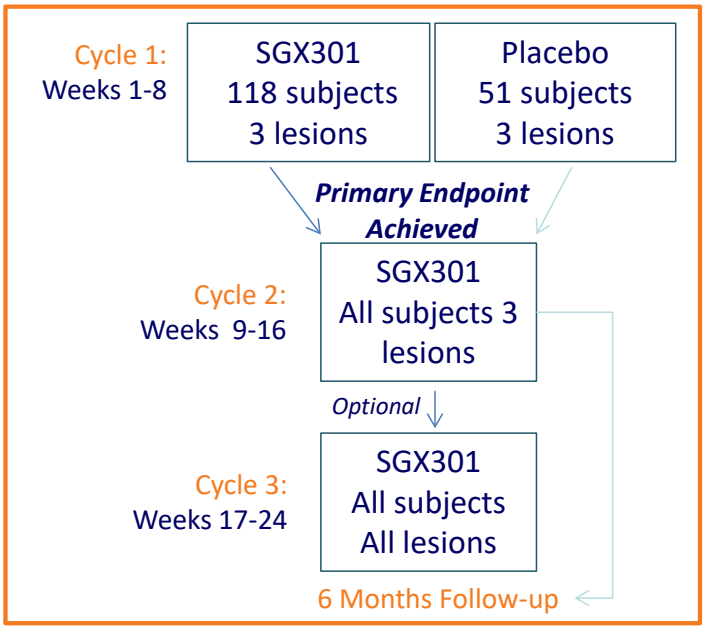


Table 1: SGX301 (topical synthetic hypericin activated with visible light) Response Rate by Subject

Lesion response was assessed with the CAILS (Composite Assessment of Index Lesions Score)[13] over 3 representative index lesions chosen at baseline and followed throughout the study.

	Placebo Response Rate (End Cycle 1)	SGX301 Response Rate (End Cycle 1)	SGX301 Response Rate (End Cycle 2)	SGX301 Response Rate (End Cycle 2) P-Value vs. Placebo in Cycle 1
Overall Response	4.0%	16.4% p<0.04	Placebo + SGX301: 22.2% SGX301 + SGX301: 40.0%	p < 0.04 p<0.0001

The response rate evaluated in Cycle 1 of this study represents a rigorously defined parameter in the context of the clinical study design. Unlike other studies, the timeline for response was measured from the first application of study drug and light (5 J/cm^2). The light dose was then increased (to a maximum of 12 J/cm^2), as dictated by the individual skin responses of the patient. It is important to note that many patients did not achieve their maximal response until mid-way through Cycle 1. Alternatively measuring response rate from the first optimal dose of drug + light, equivalent to the first application of mechlorethamine or bexarotene gel, would consequently yield an even faster assessment of onset of action.

III. SGX301 is Safe and Well Tolerated

The combination of targeted therapy with targeted light therapy using visible red-yellow spectrum light yields a very benign safety profile. SGX301 is composed of synthetic hypericin, which is not mutagenic and even when administered intravenously (IV) at much higher doses, does not cause significant adverse events other than those related to photoactivity.[16,17] Thus, the compound itself is benign. This is in stark contrast to the application of the standard therapies, e.g., topical nitrogen mustard (i.e., mechlorethamine) or oral psoralen, which are associated with mutagenesis leading to melanoma and non-melanoma skin cancers.[9,10]

The synthetic hypericin in this case is applied topically and has been shown to absorb preferentially in T-cells and even more preferentially in malignant T-cells.[18] Thus, the compound, applied 18-24 hours prior to application of light therapy, is preferentially targeted to the desired cells. Importantly, even after up to 18 weeks (36 applications) of treatment, over multiple body regions, no systemic absorption of hypericin is observed in the blood.

Overall SGX301 therapy has less cutaneous adverse events compared to bexarotene gel or mechlorethamine gel. As an example, the clinical study with mechlorethamine gel recorded a 22% discontinuation rate due to moderate or severe adverse events (AEs). 67% of drop-outs occurred within first 90 days and temporary suspension of treatment occurred in 34% of patients. Overall, 70% of patients ≥65 years of age experienced cutaneous AE and 38% discontinued treatment. Mechlorethamine treatment also created major intimacy issues for patients since treated areas of skin cannot be in contact with other people. In contrast, to date SGX301 in Study HPN-CTCL-01 has a 1% discontinuation rate due to moderate or severe AEs.

Clearly, SGX301 is safe and well tolerated and without systemic absorption. Ultimately these findings will further enhance treatment compliance.

IV. Efficacy in Deep/Thick Cutaneous Lesions

a. Folliculotropic Mycosis Fungoides

The benefits observed with SGX301 extend beyond the positive response rate and safety profile. There were several responses observed in patients with folliculotropic mycosis fungoides (MF). This is a more aggressive form of MF with malignant cells present deeper in the skin, surrounding hair follicles.[19] Lack of penetration of skin directed therapies to this deeper tissue often leads to lack of efficacy (**Figure 1**). SGX301 has maximal absorption between 500 and 650 nm in wavelength.[23] This yellow-red part of the

visible spectrum is known to penetrate significantly deeper than ultraviolet light as depicted in the Figure 1.[20] Current recommendations from the National Comprehensive Cancer Network Guidelines for the treatment of folliculotropic mycosis fungoides are to move to systemic agents due to current lack of efficacy of available skin-directed therapies.[19] The absorption spectrum of SGX301 and the clinical response observed in the current study suggest SGX301 will provide an alternative therapy for some patients with this variant of CTCL. This may allow some patients to avoid costlier and dangerous systemic therapies.

b. Efficacy in Patch and Plaque Disease

CTCL is characterized by 3 main lesion types: patches, plaques, and tumors. While tumors are uncommon in early stage disease and were excluded from the current study, patients in early stage disease can have a preponderance of either patches or plaques. Plaques are thicker lesions, and much like folliculotropic MF, have been associated with a worse prognosis.[21,22] Moreover the thickness of lesions is associated with a worsened response to skin directed therapy, including with ultraviolet light therapy.[23] In the Phase 3 study of SGX301, it was found that therapy was as effective in thicker plaques as in patches (**Table 2**), likely due to the deeper penetration of visible light (**Figure 1**).

Table 2: SGX301 Patch vs Plaque Treatment Efficacy

SGX301 Response Rate - Patches and Plaques

Contingency Test of Lesion Response Treating each Lesion as an Independent Event

	Placebo Response Rate (End Cycle 1)	SGX301 Response Rate (End Cycle 1)	SGX301 Response Rate (End Cycle 2)	SGX301 Response Rate (End Cycle 2 vs Placebo Cycle 1) P-Value Against Placebo End Cycle 1 Response Rate Against SGX301 End Cycle 1 Response Rate
Overall Lesion Efficacy	14%	21%	39%	p<0.0001 p<0.0001
Patch Lesions	17%	18%	37%	p=0.0009 p<0.0001
Plaque Lesions	11%	25%	42%	p<0.0001 p<0.0001

VI. Conclusion

In the designated patient population (patients with Stage IA, IB or IIA CTCL), the results of the Phase 3 study, including both the rapid onset efficacy (16%, p=0.04) following 6 weeks of therapy, sustained efficacy (40% response rate after 12 weeks of treatment, p<0.0001), ability to address patient populations which otherwise have been resistant to treatment (plaque lesions, folliculotropic MF) and overall safety, make this product very compelling, especially as a first-line treatment.

Bibliography

1. Munoz J. No Title. National Organization for Rare Diseases: Rare Disease Database. https://rarediseases.org/rare-diseases/mycosis-fungoides/#:~:text=Mycosis fungoides is a rare,that are composed of lymphocytes. Published 2013.

2. Berg S, Villasenor-Park J, Haun P, Kim EJ. Multidisciplinary Management of Mycosis Fungoides/Sézary Syndrome. *Curr Hematol Malig Rep*. 2017;12(3):234-243. doi:10.1007/s11899-017-0387-9

3. Hristov AC, Tejasvi T, Wilcox RA. Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2019;94(9):1027-1041. doi:10.1002/ajh.25577

4. Stern RS, Thibodeau LA, Kleinerman RA, Parrish JA, Fitzpatrick TB. Risk of Cutaneous Carcinoma in Patients Treated with Oral Methoxsalen Photochemotherapy for Psoriasis. *N Engl J Med*. 1979;300(15):809-813. doi:10.1056/NEJM197904123001501

5. Black RJ, Gavin AT. Photocarcinogenic risk of narrowband ultraviolet B (TL-01) phototherapy: early follow-up data. *Br J Dermatol*. 2006;154(3):566-567. doi:10.1111/j.1365-2133.2005.07085.x

6. Man I, Crombie IK, Dawe RS, Ibbotson SH, Ferguson J. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. *Br J Dermatol*. 2005;152(4):755-757. doi:10.1111/j.1365-2133.2005.06537.x

7. Lindahl LM, Fenger-Gron M, Iversen L. Topical nitrogen mustard therapy in patients with mycosis fungoides or parapsoriasis. *J Eur Acad Dermatology Venereol*. 2013;27(2):163-168. doi:10.1111/j.1468-3083.2011.04433.x

8. Licata AG, Wilson LD, Braverman IM, Feldman AM, Kacinski BM. Malignant melanoma and other second cutaneous malignancies in cutaneous T-cell lymphoma. The influence of additional therapy after total skin electron beam radiation. *Arch Dermatol*. 1995;131(4):432-435.

9. Nijsten TEC, Stern RS. The Increased Risk of Skin Cancer Is Persistent After Discontinuation of Psoralen+Ultraviolet A: A Cohort Study. *J Invest Dermatol*. 2003;121(2):252-258. doi:https://doi.org/10.1046/j.1523-1747.2003.12350.x

10. Vonderheid EC, Tan ET, Kantor AF, Shrager L, Micaily B, Van Scott EJ. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. *J Am Acad Dermatol*. 1989;20(3):416-428. doi:10.1016/s0190-9622(89)70051-7

11. Chung PS, Saxton RE, Paiva MB, et al. Hypericin uptake in rabbits and nude mice transplanted with human squamous cell carcinomas: study of a new sensitizer for laser phototherapy. *Laryngoscope*. 1994;104(12):1471-1476. doi:10.1288/00005537-199412000-00008

12. Tosini G, Ferguson I, Tsubota K. Effects of blue light on the circadian system and eye physiology. *Mol Vis*. 2016;22:61-72.

13. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary 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 E. *J Clin Oncol*. 2011;29(18):2598-2607. doi:10.1200/JCO.2010.32.0630

14. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149(1):25-32. doi:10.1001/2013.jamadermatol.541

15. Heald P, Mehlmauer M, Martin AG, Crowley CA, Yocum RC, Reich SD. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol*. 2003;49(5):801-815. doi:10.1016/S0190-9622(03)01475-0

16. Gulick RM, McAuliffe V, Holden-Wiltse J, et al. Phase I studies of hypericin, the active compound in St. John's wort, as an antiretroviral agent in HIV-infected adults: AIDS clinical trials group protocols 150 and 258. *Ann Intern Med*. 1999. doi:10.7326/0003-4819-130-6-199903160-00015

17. Jacobson JM, Feinman L, Liebes L, et al. Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St. John's wort plant, in patients with chronic hepatitis C virus infection. *Antimicrob Agents Chemother*. 2001. doi:10.1128/AAC.45.2.517-524.2001

18. Penjweini R, Smisdom N, Deville S, Ameloot M. Transport and accumulation of PVP-Hypericin in cancer and normal cells characterized by image correlation spectroscopy techniques. *Biochim Biophys Acta - Mol Cell Res*. 2014;1843(5):855-865. doi:https://doi.org/10.1016/j.bbamcr.2014.01.016

19. Mehta-Shah N, Horwitz SM, Ansell S, et al. Primary cutaneous lymphomas, version 2.2020. Featured updates to the NCCN guidelines. *JNCCN J Natl Compr Cancer Netw*. 2020. doi:10.6004/jnccn.2020.0022

20. Ash C, Dubec M, Donne K, Bashford T. Effect of wavelength and beam width on penetration in light-tissue interaction using computational methods. *Lasers Med Sci*. 2017;32(8):1909-1918. doi:10.1007/s10103-017-2317-4

21. Agar NS, Wedgeworth E, Crichton S, et al. Survival Outcomes and Prognostic Factors in Mycosis Fungoides/Sézary Syndrome: Validation of the Revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer Staging Proposal. *J Clin Oncol*. 2010;28(31):4730-4739. doi:10.1200/JCO.2009.27.7665

22. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. *Clin cancer Res an Off J Am Assoc Cancer Res*. 2012;18(18):5051-5060. doi:10.1158/1078-0432.CCR-12-0604

23. Gökdemir G, Barutcuoglu B, Sakiz D, Köşlü A. Narrowband UVB phototherapy for early-stage mycosis fungoides: evaluation of clinical and histopathological changes. *J Eur Acad Dermatol Venereol*. 2006;20(7):804-809. doi:10.1111/j.1468-3083.2006.01635.x

24. Fox FE, Niu Z, Tobia A, Rook AH. Photoactivated hypericin is an anti-proliferative agent that induces a high rate of apoptotic death of normal, transformed, and malignant T lymphocytes: implications for the treatment of cutaneous lymphoproliferative and inflammatory disorders. The Journal of investigative dermatology. 1998;111(2):327-32.

25. Xu L, Zhang X, Cheng W, Wang Y, Yi K, Wang Z, et al. Hypericin-photodynamic therapy inhibits the growth of adult T-cell leukemia cells through induction of apoptosis and suppression of viral transcription. Retrovirology. 2019;16(1):5.