SD-101, a Novel Class C CpG-Oligodeoxynucleotide Toll-like Receptor 9 Agonist, Given with Low Dose Radiation for Untreated Low Grade B-Cell Lymphoma: Interim Results of a Phase 1/2 Trial

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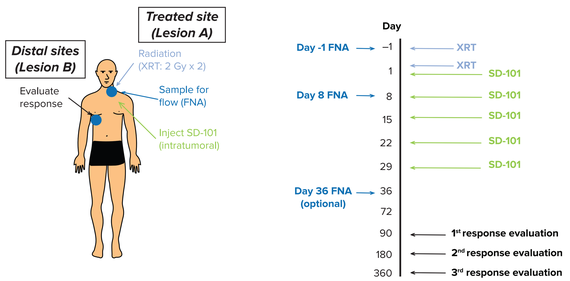
INTRODUCTION

- SD-101 is a synthetic CpG-oligodeoxynucleotide that binds to Toll-like receptor 9 (TLR9) and activates two principal TLR9 signaling pathways, leading to rapid interferon-α production and efficient generation and activation of cytotoxic CD8+ T cells.[1]
- LYM-01 is an ongoing, phase 1/2, open-label, two-part study assessing the effects of intratumoral SD-101 injection, in combination with low-dose radiation, on low-grade non-Hodgkin's B-cell lymphoma (NHL).
- In Part 1 of the trial, a phase 1 dose-escalation study, four cohorts of patients with NHL (n=3 per cohort) received SD-101 at 1 mg, 2 mg, 4 mg, or 8 mg according to a standard 3 + 3 design.
- As reported previously,[2] results from Part 1 showed that direct injection of SD-101 into tumors, in combination with low-dose radiation, was well tolerated in patients with low-grade NHL. No dose-limiting toxicities were observed in any SD-101 dose cohort (1–8 mg), nor was a maximum tolerated dose identified.
- The most common treatment-related adverse events (TEAEs) were local injection-site reactions and flu-like symptoms, including fever, chills and myalgia. Nearly all AEs were low grade, and no serious TEAEs related to SD-101 treatment were reported.
- SD-101 induced a significant antitumor response across all dose groups, not only at the injected tumor, but at other non-injected lesions as well (abscopal effect).
- The current poster provides recent follow-up data on patients from Part 1. It also provides data for the first time on patients who participated in Part 2 of the trial, an ongoing phase 2 dose-expansion study.

METHODS

- Eligible patients had biopsy-confirmed, untreated, low-grade B-cell lymphoma (follicular, marginal, or chronic lymphocytic leukemia/small lymphocytic lymphoma) with lymph node involvement (appropriate candidates for "watch and wait").
- Patients also had an ECOG performance status of 0 or 1 and at least two sites of measurable disease: one for intratumoral injection (Lesion A); and a second not included in the radiation field of the first (Lesion B) (**Figure 1**).
- Lesion A was treated with low-dose radiation (XRT; 2 Gy) on Day –1 and 1 and was injected with SD-101 on Day 1, 8, 15, 22, and 29 (**Figure 1**). Lesion B received no treatment.
- In Part 1 of the study (phase 1 dose escalation), four dose cohorts (n=3 per cohort) received SD-101 at 1 mg, 2 mg, 4 mg, or 8 mg according to a standard 3 + 3 design.
- In Part 2 of the study (phase 2 expansion), patients were enrolled in two dose cohorts to receive SD-101 at 1 mg or 8 mg. Original enrollment targets were n=6 per dose cohort, with an option to enroll an additional 6 patients in either group per Sponsor decision.

Figure 1. Study Schema



OBJECTIVES

- To assess the immune-cell profile at treated lesions, and to correlate the profile with any abscopal antitumor effect, fine needle aspirates (FNA) were collected from Lesion A in follicular lymphoma patients 8 days after the start of treatment (i.e., following one SD-101 injection) and assessed by flow cytometry.
- Response was assessed by CT (or CT/PET) and bone marrow biopsy at Month 3, Month 6, and every 6 months thereafter according to Cheson criteria.[3] Response was determined at both the treated lesion (Lesion A) and at untreated lesions (up to 5 total; Lesion B–F inclusive) to assess local and abscopal effects, respectively.
- Safety was assessed by treatment-emergent adverse events (TEAEs), serious TEAEs, vital signs, electrocardiogram, hematology, and blood chemistry. The data cutoff for safety assessments was October 3, 2016.

RESULTS

Table 1. Demographics and Baseline Characteristics

	SD-101 Dosage				
	1 mg (n=9)*	2 mg (n=3)	4 mg (n=3)	8 mg (n=13)*	All (n=28)
Age, mean year (SD)	60.8 (6.1)	56 (9.5)	61 (16.5)	62.7 (12.3)	61.2 (10.5)
Male, n (%)	6 (66.7)	1 (33.3)	2 (66.7)	7 (53.8)	16 (57.1)
Race, n (%)					
White	8 (88.9)	3 (100)	3 (100)	12 (92.3)	26 (92.9)
Other	1 (11.1)	0	0	1 (7.7)	2 (7.1)
ECOG PS, n (%)					
0	6 (66.7)	3 (100)	3 (100)	11 (84.6)	23 (82.1)
1	3 (33.3)	0	0	2 (15.4)	5 (17.9)
Disease Type, n (%)					
CLL	0	0	1 (33.3)	0	1 (3.6)
Follicular	7 (77.8)	3 (100)	2 (66.7)	8 (61.5)	20 (71.4)
Marginal nodal	1 (11.1)	0	0	3 (23.1)	4 (14.3)
SLL	1 (11.1)	0	0	1 (7.7)	2 (7.1)
Other	0	0	0	1(7.7)	1 (3.6)
Stage, n (%)					
I	0	0	1 (33.3)	0	1 (3.6)
II	1 (11.1)	0	0	3 (23.1)	4 (14.3)
III	6 (66.7)	1 (33.3)	1 (33.3)	3 (23.1)	11 (39.3)
IV	2 (22.2)	2 (66.7)	1 (33.3)	7 (53.9)	12 (42.9)
Grade, n (%)					
1	1 (11.1)	3 (100)	2 (66.7)	6 (46.2)	12 (42.9)
2	6 (66.7)	0	1 (33.3)	2 (15.4)	9 (31.4)
3A	1 (11.1)	0	0	0	1 (3.6)
Unknown	1 (11.1)	0	0	5 (38.5)	6 (21.4)
FLIPI Score, n (%)					
n	7	3	2	8	20
0	0	0	0	1 (12.5)	1 (5.0)
1	2 (28.6)	0	0	1 (12.5)	3 (15.0)
2	3 (42.9)	3 (100)	1 (50.0)	3 (37.5)	10 (50.0)
3	2 (28.6)	0	1 (50.0)	3 (37.5)	6 (30.0)

*Contains patients from Part 1 and Part 2.
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; SD, standard deviation; SLL, small lymphocytic leukemia.

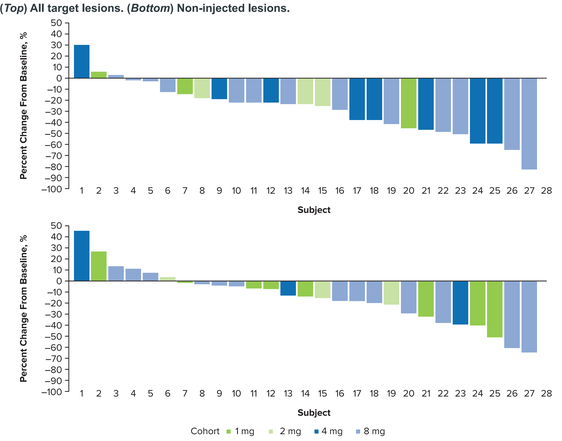
Table 2. Response Summary

Disease	Response	Overall Response, n (%)				
		1 mg*	2 mg	4 mg	8 mg*	Total
CLL	n	0	0	1	0	1
	SD			1 (100)		1 (100)
	PR+CR			0		0
Follicular	n	7	3	2	8	20
	CR	0	0	0	0	0
	PR	2 (28.6)	0	0	1 (12.5)	3 (15.0)
	SD	5 (71.4)	3 (100)	1 (50.0)	7 (87.5)	16 (80.0)
	PD	0	0	1 (50.0)		1 (5.0)
	PR+CR	2 (28.6)	0	0	1 (12.5)	3 (15.0)
Marginal Nodal	n	1	0	0	3	4
	SD	0			3 (100)	3 (75.0)
	PD	1 (100)			0	1 (25.0)
	PR+CR	0			0	0
SLL	n	1	0	0	1	2
	SD	1 (100)			1 (100)	2 (100)
	PR+CR	0			0	0
Other	n	0	0	0	1	1
	PD				1 (100)	1 (100)
	PR+CR				0	0
All Disease	n	9	3	3	13	28
	CR	0	0	0	0	0
	PR	2 (22.2)	0	0	1 (7.7)	3 (10.7)
	SD	6 (66.7)	3 (100.0)	2 (66.7)	11 (84.6)	22 (78.6)
	PD	1 (11.1)	0	1 (33.3)	1 (7.7)	3 (10.7)
	PR+CR	2 (22.2)	0	0	1 (7.7)	3 (10.7)

*Contains patients from Part 1 and Part 2.
CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SLL, small lymphocytic leukemia.

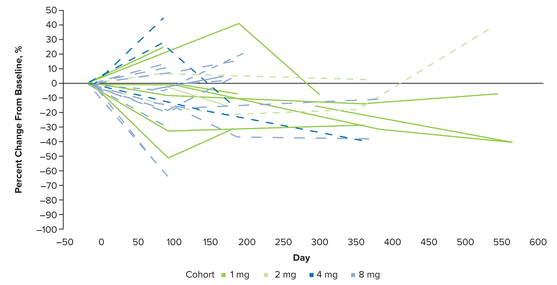
Figure 2. Best Percent Change in Tumor Burden

(*Top*) All target lesions. (*Bottom*) Non-injected lesions.



Subject 001019 (Follicular/1 mg) was excluded due to missing baseline data.

Figure 3. Percent Change from Baseline in Tumor Burden Over Time in Non-Injected Lesions



Subject 001019 (Follicular/1 mg) was excluded due to missing baseline data.

Figure 4. A Higher Percentage of CD8+ T Cells in Treated Lesions Corresponds with Increased Abscopal Response

Shown are percentages of live cells that were CD8+ T cells in their respective FNA samples from Lesion A. The best abscopal response was captured at the time the analysis was done (day post treatment ranged from day 90 to day 540). (A). For the abscopal clinical response, range is represented from red (highest percentage decrease in tumor size from study start) to green (lowest). For the percentage of live cells that are CD8+ T cells, range is represented from red (highest percentage) to green (lowest). B. Plot of data from A.

A

Abscopal Best Response (%)	% live cells: CD8 T cells
–51.8	12.67
–49.1	16.65
–41.0	10.84
–39.2	17.48
–38.0	5.60
–32.8	8.09
–19.0	8.69
–18.5	5.26
–15.8	4.20
–7.1	5.22
2.6	9.83
22.5	26.84
44.6	4.44

B

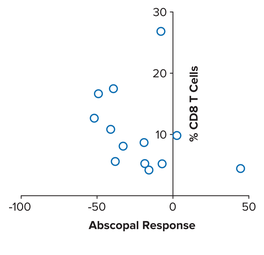


Table 3. Treatment-Emergent Adverse Events

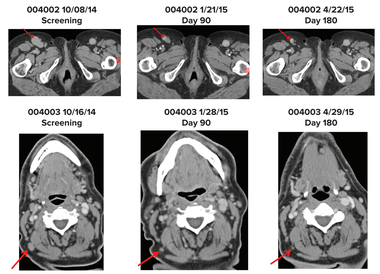
Subjects With at Least 1 TEAE	SD-101 Dosage				
	1 mg (n=9)	2 mg (n=3)	4 mg (n=3)	8 mg (n=13)	Total (n=28)
All TEAEs	9 (100)	3 (100)	3 (100)	13 (100)	28 (100)
Grade 3–4 TEAEs	2 (22.2)	0	1 (33.3)	6 (46.2)	9 (32.1)
Serious TEAEs	0	0	1 (33.3)	0	1 (3.6)
Treatment-related TEAEs	9 (100)	3 (100)	3 (100)	13 (100)	28 (100)
Grade 3–4 treatment-related TEAEs	2 (22.2)	0	0	6 (46.2)	8 (28.6)
TEAEs leading to discontinuation	0	0	0	1 (7.7)	1 (3.6)
TEAEs leading to death	0	0	0	0	0
Dose-limiting toxicities	0	0	0	0	0
Most frequent TEAEs (> 20%)					
Fatigue	8 (88.9)	3 (100.0)	3 (100.0)	12 (92.3)	26 (92.9)
Malaise	8 (88.9)	2 (66.7)	3 (100.0)	13 (100.0)	26 (92.9)
Chills	7 (77.8)	2 (66.7)	3 (100.0)	13 (100.0)	25 (89.3)
Myalgia	6 (66.7)	3 (100.0)	3 (100.0)	13 (100.0)	25 (89.3)
Headache	7 (77.8)	3 (100.0)	3 (100.0)	11 (84.6)	24 (85.7)
Pyrexia	4 (44.4)	1 (33.3)	2 (66.7)	12 (92.3)	19 (67.9)
Nausea	1 (11.1)	1 (33.3)	0	8 (61.5)	10 (35.7)
Diarrhea	3 (33.3)	0	1 (33.3)	4 (30.8)	8 (28.6)
Injection site erythema	4 (44.4)	0	1 (33.3)	3 (23.1)	8 (28.6)
Vomiting	0	1 (33.3)	0	5 (38.5)	6 (21.4)
Grade 3–4 TEAEs					
Malaise	0	0	0	5 (38.5)	5 (17.9)
Headache	1 (11.1)	0	0	4 (30.8)	5 (17.9)
Chills	0	0	0	4 (30.8)	4 (14.3)
Myalgia	0	0	0	3 (23.1)	3 (10.7)
Fatigue	0	0	0	2 (15.4)	2 (7.1)
Neutropenia	0	0	0	1 (7.7)	1 (3.6)
Neutrophil count decreased	1 (11.1)	0	0	0	1 (3.6)
Pulmonary embolism	0	0	1 (33.3)	0	1 (3.6)

TEAE, treatment-emergent adverse event.

- As in Part 1 (dose escalation), the most common treatment-related TEAEs in Part 2 (expansion) were flu-like symptoms (**Table 3**):
  - All events of flu-like symptoms resolved with acetaminophen or ibuprofen, typically within ≤48 hours
  - Twenty-nine Grade 3 transient flu-like symptoms were reported in four patients (44%) who received the 8-mg dose (e.g., chills, headache, malaise, myalgia, and fatigue)
  - Only two of the four patients experienced all 5 Grade 3 flu-like symptoms after intratumoral injection
- One patient (1 mg) had a dose delay attributable to Grade 3 neutropenia; the event resolved following drug interruption and the patient completed dosing.
- Two patients tolerated a second cycle of 1 mg x 5 injections without any unexpected toxicity.
- No Grade 4 TEAEs were reported. One serious TEAE was reported in the 4-mg cohort (Grade 3 pulmonary embolism; unrelated), and 1 patient discontinued due to Grade 3 malaise and Grade 2 myalgia.

Figure 5. CT Scans Pre- and Post-Treatment With SD-101 in Combination With Low-Dose Radiation

Arrows mark the treated lesions. Top row, patient 4002; bottom row, patient 4003.



CONCLUSIONS

- Intratumoral SD-101 injection of a lymphoma lesion (Lesion A) following low-dose, local, lesion-specific radiation therapy showed promising preliminary efficacy. Tumor burden decreased in a majority of patients at the radiated + injected site and at untreated site(s) (Lesion B), where durable responses were documented (i.e., abscopal anti-tumor activity).
- Intratumoral injection of SD-101 at doses of 1 mg, 2 mg, 4 mg, and 8 mg using the schedule described in the study schema was well tolerated. TEAEs consisted mainly of Grade 1–2 flu-like symptoms or local site reactions, with a trend toward Grade 3 events at the highest tested dose.
- Based on preliminary data, abscopal anti-tumor activity correlated with a higher percentage of CD8+ T cells in the treated lesion.

REFERENCES AND DISCLOSURES

1. SD-101. Available from: http://www.dynavax.com/our-pipeline/cancer-immunotherapy/sd101/. 2. Levy R et al. *Cancer Res.* 2016;76(14 Supplement):CT047-CT. 3. Cheson BD et al. *J Clin Oncol.* 2007;25(5):579-86.

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