VSLI (vincristine sulfate liposomes injection) in the Treatment of Adult Subjects with Advanced, Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL): A Combined Analysis of the VSLI-06 and rALLy Studies

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Abstract #2143

Background: The outcome of adults with relapsed/refractory ALL, and of those whose disease recurs after first salvage, in particular, is extremely poor. Second salvage therapy with single agents has historically produced a complete response (CR) in only 4% of patients. (O'Brien, S, et al. Cancer 2008; 113:3186-3191). Third salvage therapy has not been studied but would be expected to be even less effective. Conventional vincristine sulfate (VCR) is an effective anti-leukemia agent, widely used in the treatment of ALL as part of several intensive regimens. VCR is dosed at 1.4 mg/m^2 with a 2 mg cap due to early onset of peripheral neuropathy. VSLI (Marqibo®) is a nano-particle encapsulated formulation of VCR designed to facilitate dose intensification, improve duration of drug exposure, and enhance cancer and bone marrow drug delivery.

Methods: Two distinct studies investigated VSLI in adult patients with advanced, relapsed/refractory ALL. Study VSLI-06 was a Phase 1/2, multi-center, 36 patient, dose-escalation study to determine safety, maximum tolerated dose, and anti-leukemia activity. Patients received VSLI intravenously (IV) weekly at doses of 1.5, 1.825, 2.0, 2.25 or 2.4 mg/m^2 with no dose cap plus dexamethasone 40 mg on days 1-4 and 11-14 of each 4 week course. The rALLy Study was a Phase 2, multi-national, 65 patient study of single-agent VSLI (2.25 mg/m^2 IV weekly without dose cap) in adults with ALL in second relapse or who had progressed following at least two prior lines of anti-leukemia therapy. All subjects had been previously treated with VCR, and all received at least one dose of VSLI. The median age in both studies was 32 years with a combined range of 19 to 83 years. Other than one subject in VSLI-06, all subjects were Philadelphia chromosome negative.

Results: The combined overall response rate was 31% (31 of 101). The combined complete response (CR) rate including CR with incomplete platelet (CRp) or hematologic (CRi) recovery was 20% (20/101). This response rate was consistent across the studies (19.4% and 20%, respectively). Hematologic improvement (HI) was achieved in 4 patients (11%) in VSLI-06 and 9 (14%) in RALLY, thus reducing transfusions and hospital visits. Five patients were able to receive a post-VSLI hematopoietic stem cell transplant (HSCT) in VSLI-06, and 10 patients were able to receive a post-VSLI HSCT in rALLy. The table below summarizes key study characteristics.

Characteristic	VSLI-06 N = 36	rALLy N = 65	COMBINED N = 101
Extramedullary Disease, N (%)	3 (8)	13 (20)	16 (16)
Prior HSCT, N (%)	6 (17)	31 (48)	37 (37)
ECOG 2 or 3, N (%)	7 (19)	15 (23)	22 (22)
Lines of Therapy prior to VSLI, N (%)			
1	13 (36)	0	13 (13)
2	15 (42)	36 (55)	51 (51)
3	8 (22)	21 (32)	29 (29)
4	0	7 (11)	7 (7)
5	0	1 (2)	1 (1)

The most commonly reported safety events in the studies were similar and included constipation, neuropathy, fatigue, nausea, pyrexia, febrile neutropenia, and anemia.

Conclusions: These two studies totaling 101 patients with similar populations of advanced relapsed/refractory ALL showed a combined 20% CR/CRp/CRi rate, dwarfing the rate in historical studies. This is particularly encouraging, given that 100% of subjects had received prior VCR and that historical control data were largely in a less heavily pre-treated population. Both VSLI alone and combined with pulse dexamethasone appear to be highly active. In total, 15% of combined study patients were able to "bridge" to HSCT. Use of VSLI in the frontline setting and in combination regimens should further improve ALL patient outcomes.

Background

- Despite achievement of an initial remission, the vast majority of adults with acute lymphoblastic leukemia (ALL) relapse
- First salvage chemotherapy induces complete remission (CR) in 21% to 31% with a median CR duration of 2-7 months[1]
- Outcome of adults with ALL who develop recurrence after first salvage or shortly after stem cell transplantation is extremely poor
- Second salvage chemotherapy, typically multi-agent, induces CR in up to 18% of subjects with a median overall survival of 3 months and up to a 23% incidence of early/induction death[2]
- Single agent second salvage therapy induces CR in 4% (single institution retrospective analysis)[2]
- Treatment of ALL beyond the second salvage setting has not been well characterized and response rates would be expected to be negligible
- Vincristine (VCR) has dose-dependent activity against hematologic malignancies, is generally dosed at 1.4 mg/m^2 yet capped at 2 mg due to neurotoxicity
- VSLI is a liposome-encapsulated vincristine sulfate dosed at 2.25 mg/m^2 without a dose cap

Study Designs

	VSLI-06[3]	HBS-407 (rALLy)
Study Type	Single-arm, Dose-escalation, Phase 1/2 Study 3 centers; U.S. based	Single-arm, Open-label, Phase 2 Study 35 centers; global
Study Population	Previously treated or refractory ALL including lymphoblastic lymphoma (LL) and Burkitt's subtypes ECOG PS ≤ 3 All ages were eligible	Ph- ALL or LL in second relapse or having progressed following two treatment lines of chemotherapy with at least one prior CR ≥ 90 days ECOG PS ≤ 3 Age ≥ 18 years
VSLI Dosing	1.5, 1.825, 2.0, 2.25, and 2.4, mg/m^2 IV on Days 1, 8, 15, and 22 of a 28-day course	2.25 mg/m^2 IV (MTD from VSLI-06 Study) on Days 1, 8, 15, 22 of a 28-day course
Concomitant Anti-Leukemic Therapy	Dexamethasone 40 mg daily either orally or IV on Days 1-4 and 11-14 of a 28-day course	None
Major Study Endpoints	MTD of VSLI in combination with Dexamethasone Efficacy (CR/CRp) Safety and Tolerability	Efficacy (CR/CRi) CR/CRi duration Overall Survival Safety and Tolerability

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Disclosure: A. Hagey, G. Messerschmidt and S. Deitcher are employed by Talon Therapeutics, Inc.

Subject Demographics

Characteristic	VSLI-06 (N = 36)	rALLy (N = 65)	Combined (N=101)
Median Age (range)	32 (19-62)	32 (19-83)	32 (19-83)
Male (%) / Female (%)	12 (33) / 24 (67)	33 (51) / 32 (49)	45 (44) / 56 (56)
B cell lineage ALL, N (%) T cell lineage ALL, N (%) Burkitt-like lymphoma, N (%) T lymphoblastic lymphoma, N (%)	31 (86) 3 (8) 2 (6)	55 (84) 9 (14) - 1 (2)	86 (85) 12 (12) 2 (2) 1 (1)
ECOG PS 2-3, N (%)	7 (19)	15 (23)	22 (22)
Extramedullary Disease, N (%)	3 (8)	13 (20)	16 (16)
Prior VCR Exposure, N (%)	36 (100)	65 (100)	101 (100)
Lines of Prior Therapy* 1 2 3 4 5 6	 13 (36) 15 (42) 8 (22) 0 (0) 0 (0) 0 (0)	 0 33 (51) 23 (35) 8 (12) 0 (0) 1 (2)	 13 (13) 48 (47) 31 (31) 8 (8) 0 (0) 1 (1)
Prior Stem Cell Transplant, N (%)	6 (17)	31 (48)	37 (37)

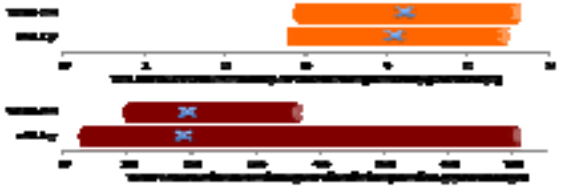
*Lines of Prior Therapy from rALLy study reflects updated data

Efficacy

Response Category	VSLI-06 (N = 36)	rALLy (N = 65)	Combined (N = 101)
Complete Response, N (%) (CR and CRp or CRi)	7 (19) CR + CRp	13 (20) CR + CRi	20 (20) CR + CRp + CRi
Bone Marrow Blast Response, N (%)	N/A	4 (6)	--
Partial Response, N (%)	1 (3)	6 (9)	7 (7)
Overall Response Rate, N (%) (CR + BMB + PR)	8 (22)	23 (35)	31 (31)
Hematologic Improvement, N (%)	4 (11)	9 (14)*	13 (13)
Stable Disease/No Response, N (%)	13 (36)	13 (20)	26 (26)
Progressive Disease, N (%)	9 (25)	19 (29)	28 (28)

*HI assessed in addition to primary response criteria

Intensive Dose Delivery



VSLI Facilitated Bridge to Stem Cell Transplant (SCT)

15% of Relapsed/Refractory ALL subjects given VSLI were able to receive potentially curative SCT

- 5 of 36 subjects in VSLI-06 proceeded to SCT
- 10 of 65 subjects in rALLy proceeded to SCT

Safety and Tolerability

The most common toxicities experienced on the rALLy study and corresponding rates for the VSLI-06 study are similar to those experienced with standard vincristine and by subjects with hematologic malignancies and are listed in the table below.

Adverse Event	VSLI-06 Study, All Grades (N=36)	rALLy Study, All Grades (N=65)	Combined Rate (N=101)
Appetite Decreased, N (%)	9 (25)	23 (34)	32 (32)
Constipation, N (%)	24 (67)	34 (52)	58 (57)
Diarrhea, N (%)	15 (42)	22 (34)	37 (37)
Febrile Neutropenia, N (%)	14 (39)	25 (39)	39 (39)
Nausea, N (%)	17 (47)	31 (47)	48 (48)
Peripheral Neuropathy/Neuropathy, N (%)	18 (50)	41 (63)	59 (58)
Pyrexia, N (%)	16 (44)	25 (39)	41 (41)

Events on VSLI-06 with incidence >40% included: Fatigue (61%), Anemia (50%), Insomnia (47%), Abdominal Pain (44%), Thrombocytopenia (44%) and Hyperglycemia (42%)

Conclusions

- VSLI demonstrated encouraging activity in advanced ALL as both a single agent and in combination with dexamethasone
  - Combined overall response rate of 31%
  - Combined overall CR + CRi + CRp rate of 20%
  - Favorable anti-leukemia activity compared with the published single agent second salvage experience[3]
- VSLI facilitated a bridge to transplant in 15% of subjects in the combined analysis
- VSLI safety profile was predictable and manageable even in subjects with residual/prior peripheral neuropathy
- VSLI facilitated VCR dose-intensification
  - Higher dose per m^2 and lack of dose cap compared to common standard VCR dosing
  - Individual doses up to 5.7 mg and acute cumulative doses up to 70.1 mg were delivered
- Additional studies of VSLI are planned or ongoing
  - Phase 3, comparative trials of VSLI vs. VCR in de novo elderly ALL and elderly aggressive lymphoma
  - Phase 1 dose-finding and PK trial of VSLI in pediatric solid tumors/leukemia

References

[1]Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. Cancer 1999;86:1216-30.
[2]O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. Cancer 2008;113:3186-91.
[3]Thomas DA, Kantarjian HM, Stock W, et al. Phase 1 multicenter study of vincristine sulfate liposomes injection and dexamethasone in adults with relapsed or refractory acute lymphoblastic leukemia. Cancer 2009; 115:5490-5498.

This poster can be found at http://www.talontx.com

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