SL-401, A Targeted Therapy Directed to the Interleukin-3 Receptor Present On Leukemia Blasts and Cancer Stem Cells, Is Active As a Single Agent in Patients with Advanced AML

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Background: SL-401 is a novel biologic targeted therapy, comprised of human IL-3 coupled to a truncated diphtheria toxin payload that inhibits protein synthesis, directed at the interleukin-3 receptor (IL-3R). IL-3R is overexpressed on leukemia blasts and cancer stem cells (CSCs) relative to normal hematopoietic cells. Since SL-401 uniquely targets both the leukemia blasts (tumor bulk) and CSCs, it would be expected to induce tumor regression (anti-tumor bulk effect), as well as inhibit tumor repopulation (anti-CSC effect), thereby improving survival. SL-401 has been evaluated in a Phase 1/2 clinical trial in patients with advanced hematologic cancers. In this study, SL-401 has demonstrated objective clinical responses, including durable complete responses (CRs) and protracted overall survival (OS) in patients with heavily pretreated AML. The current report is a final analysis of the patients with AML or MDS.

Study Design: Seventy-eight patients with advanced hematologic cancers, including relapsed or refractory AML (n = 59), de novo AML unfit for chemotherapy (n = 11), high-risk MDS (n = 7), and other (n = 1), were enrolled in a multicenter study. Among the patients with relapsed or refractory AML, the numbers of patients receiving SL-401 as 2nd, 3rd, or >3rd line therapy were 24, 16, and 19, respectively. The median (range) age for AML patients was 65 (7, 84) years.
Patients received SL-401 as a 15-minute intravenous infusion in one of two dosing regimens for a single cycle to determine the maximum tolerated dose (MTD) and assess antitumor activity. In Regimen A, 45 patients received doses ranging from 4 to 12.5 μg/kg every other day for up to 6 doses. In Regimen B, 33 patients received doses ranging from 7.1 to 22.1 μg/kg daily for up to 5 doses.

**Results:** A single cycle of SL-401 demonstrated single agent activity in patients with relapsed or refractory AML, including 2 durable CRs of 8 and >25 months duration and 5 partial responses (PRs). OS was also notable among patients who received one cycle of SL-401 as ≥3rd line therapy for AML; the median OS was 3.6 (2.3, 6.1) months. Moreover, at therapeutically relevant doses, defined as the MTD or one or two dose levels below the MTD (9.4, 12.5, or 16.6 μg/kg/day), the median OS among AML patients who received SL-401 as ≥3rd line therapy (n = 16) was 5.6 (2.5, 10.8) months. These OS values compared favorably to historical results of 1.5 months for patients treated with standard chemotherapy.

SL-401 was well tolerated. The MTD was not achieved with Regimen A, whereas the MTD for Regimen B was 16.6 μg/kg/day, with manifestations of capillary leak syndrome, including hypoalbuminemia and edema, as the dose-limiting toxicity (DLT) at the 22.1 μg/kg/day dose level. Transient (i.e., lasting ≤2 weeks) transaminase elevations were among the most common Grade 3 AEs. Notably, there was no evidence of treatment-related bone marrow suppression.

**Conclusion:** SL-401 demonstrated single agent anti-tumor activity and was well tolerated in patients with advanced AML. Improved survival was observed among patients who received a single cycle of SL-401 as ≥3rd line treatment, a disease setting in which there is no standard therapy. SL-401 may be an attractive treatment option for these patients given their tendency to be myelosuppressed and therefore are often poor candidates for myelosuppressive therapies that have limited benefit on clinical response and survival in this setting.

Based on these positive findings, SL-401 will be advanced into a randomized Phase 2b trial to treat patients with AML in the 3rd line setting. Patients will be randomized to treatment with either multiple cycles of SL-401 or physician’s choice, which will consist of available standard therapeutic agents. In addition, the efficacy and safety of SL-401-based combination therapy will also be studied in earlier lines of AML given the lack of overlapping toxicities with existing hematologic cancer therapies.