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## **SM09419, a Novel, Small-Molecule CDC-like Kinase (CLK) Inhibitor, Demonstrates Strong Inhibition of the Wnt Signaling Pathway and Antitumor Effects in Mantle Cell Lymphoma Models**

Heekyung Chung, PhD<sup>1</sup>, Emily Creger<sup>1</sup>, Lauren Sitts, MS<sup>1</sup>, Kevin Chiu<sup>1</sup>, Chi-Ching Mak, PhD<sup>1</sup>, Sunil KC, PhD<sup>1</sup>, Betty Tam, PhD<sup>2</sup>, Gail Buccì<sup>1</sup>, Josh Stewart<sup>1</sup>, Timothy Phalen, PhD<sup>1</sup>, Steven Cha, MD<sup>1</sup>

<sup>1</sup>Samumed, LLC, San Diego, CA

<sup>2</sup>Formerly Samumed, LLC

**Background:** Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma (NHL) that accounts for ~7% of all NHL in the U.S. MCL is associated with aberrant activation of the Wnt signaling pathway, which plays a key role in the survival and maintenance of MCL-initiating cells. Many MCL patients experience relapse and subsequent disease progression due to chemoresistance following initial therapy; hence, novel therapies are needed. CLKs regulate the activity of serine/arginine-rich splicing factors (SRSFs) that modulate spliceosome assembly, mRNA splicing, and gene expression. SM09419 is a novel, oral, small-molecule pan-CLK inhibitor that potently inhibits the Wnt pathway. The purpose of these studies was to examine the antitumor activity of SM09419 in preclinical models of MCL.

**Methods and Results:** SM09419 potently inhibited both CLK1–CLK4 (IC<sub>50</sub> for all <0.02 μM) and Wnt signaling pathway (average EC<sub>50</sub>=0.068 μM) activities. In REC-1 and GRANTA-519 MCL cells, SM09419 dose-dependently inhibited SRSF6 phosphorylation and potently suppressed expression of Wnt-related genes (*CCND1*, *LEF1*, *TCF7*) and proteins vs. vehicle. In tests on 5 MCL cell lines, cell proliferation was strongly impaired by SM09419 across all lines (average EC<sub>50</sub>=0.102 μM [0.021–0.236]). SM09419 also induced apoptosis in REC-1 and GRANTA-519 cells, increasing caspase 3/7 activation and PARP cleavage while reducing survivin and MCL-1 expression vs. vehicle.

*In vivo* antitumor effects and tolerability of oral SM09419 (QD 20–21 days) were assessed in mice bearing REC-1 and JeKo-1 flank xenografts (n=5/group). In REC-1 xenografts, strong tumor growth inhibition (TGI) vs. vehicle occurred in mice treated with 12.5, 25, and 50 mg/kg SM09419 (TGI 88% [*P*<0.01], 100%, and 100% [*P*<0.001], respectively), and the two highest doses induced complete tumor regression in all mice from D14. Similarly, in JeKo-1 xenografts, SM09419 (12.5 and 25 mg/kg) induced significant TGI vs. vehicle (71% and 100%, respectively; *P*<0.0001) with complete tumor regression at 25 mg/kg, whereas acalabrutinib (50 mg/kg BID) was not efficacious (27% TGI) when tested in parallel. SM09419 25mg/kg induced reversible suppression of phospho-SRSF6 protein and inhibited Wnt pathway-related gene expression (*TCF7* and *DVL2*) in JeKo-1 tumors in a single-dose PD study, demonstrating downstream target engagement *in vivo*. SM09419 was also assessed in 2 patient-derived xenograft (PDX) mouse models of MCL. PDX cells were injected intravenously and treatment was initiated upon 8%–12% engraftment of human CD45+CD19+ cells in peripheral blood. In the first model, derived

from a patient who was progressive after 8 modalities including ibrutinib, SM09419 (25 mg/kg QD) increased survival vs. vehicle (100% through D26 vs. 0% by D12, respectively; n=6/group) and suppressed MCL engraftment in the blood (12% at D26 vs. 69% at D8 and D12, respectively;  $P=0.002$ ) and bone marrow (30% at D26 vs. 91% at D8 and D12, respectively;  $P=0.002$ ). In the second model, derived from a patient refractory after ibrutinib and anti-PDL1 treatment, SM09419 (25 mg/kg QD) significantly suppressed MCL engraftment vs. vehicle in the blood (8% vs. 72%), bone marrow (20% vs. 57%), and spleen (15% vs. 96%) at D28 (study end;  $P<0.001$  for all; n=4/group). In addition, SM09419 greatly inhibited splenomegaly vs. vehicle (0.04 g vs. 0.4 g, respectively;  $P<0.001$ ). In a subsequent experiment in the same model, mice (n=7/group) were treated with 12.5 or 25 mg/kg SM09419 or vehicle for 12 weeks (to D85). Blood MCL engraftment at D41 was significantly lower in mice treated with SM09419 (40% at 12.5 mg/kg and 23% at 25 mg/kg) vs. vehicle (88%;  $P<0.01$  and  $P<0.001$ , respectively). SM09419 dose-dependently increased survival (28.6% at 12.5 mg/kg and 85.7% at 25 mg/kg at D85) vs. vehicle (0% at D63); survival was maintained in both dose groups during post-treatment monitoring (to D99). SM09419 was well tolerated in all tested mouse models based on body weight measurements.

**Conclusion:** In summary, SM09419 potently inhibited SRSF6 phosphorylation, Wnt signaling pathway activity, and cell proliferation and induced apoptosis in MCL cell lines. The strong *in vivo* antitumor effects observed as a single agent suggest that SM09419 may provide a clinical benefit for patients with treatment-resistant or refractory MCL. A Phase 1 study assessing safety, tolerability, and pharmacokinetics of SM09419 in subjects with advanced hematologic malignancies is being initiated.