CDK9 Inhibition Enhances Venetoclax Activity and Prolongs Survival in a T-PLL PDX model

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INTRODUCTION

T-cell prolymphocytic leukemia (T-PLL) is a rare and deadly mature leukemia with few treatment options and adverse prognosis. Currently there is no effective treatment for patients with relapsed disease, with an overall survival of less than 6 months. Our group demonstrated a strong T-PLL dependency on the BCL2family of antiapoptotic proteins using BH3 profiling in patient samples (2023, ASH Annual Meeting, #4192). We generated an *in vivo* T-PLL patient derived xenograft (PDX)model by engrafting a relapsed/refractory T-PLL patient sample into NSG (NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/*SzJ*) mice. This model reproduces key human clinicopathological features of T-PLL. The model was expanded and used in a pre-clinical trial to evaluate a novel therapeutic combination using SLS009(GFH009), a specific CDK9 inhibitor and Venetoclax, a BCL2inhibitor. These drugs inhibit separate, but partially overlapping signaling pathways covering BCL2, MCL1 and MYC.

AIMS

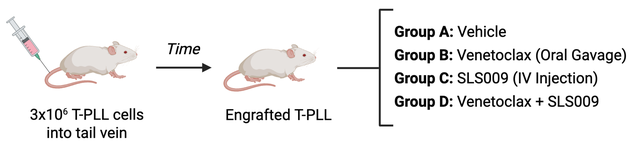
1. Expand T-PLL PDX model and use in a pre-clinical trial to evaluate a novel therapeutic combination.
2. Evaluate the effect of Venetoclax (BCL2 inhibitor) and SLS009(CDK9 inhibitor) independently and in combination on the overall survival and tumor progression.

METHODS

PDX T-PLL mice model was generated by injecting 3x10^6 patient derived cells via tail vein in NSG mice. Mice injected with PDX T-PLL cells via tail vein were monitored using flow cytometry to detect hCD45+ cells in peripheral blood (PB).

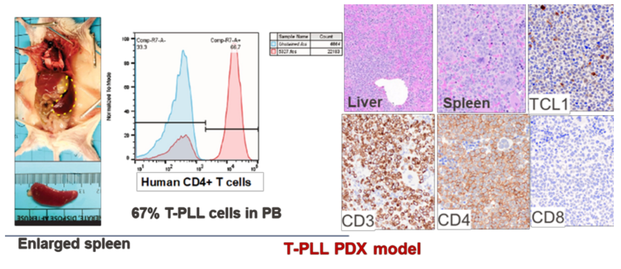
Mice were treated once total human CD45 positive cells reached 5% in PB.

Venetoclax (25mg/kg) was administered via oral gavage once daily for 2 weeks with 2-day rest. SLS009 (10mg/kg) was administered via tail vein injection two days a week for 6 weeks. We evaluated the effects of this drugs independently and in combination on the percentage T-PLL on PB and on the overall survival.



RESULTS

Newly established PDX model reproduces key clinical and pathological features of human T-PLL: A relapsed/refractory T-PLL patient sample was successfully engrafted in NSG mice. The PDX mice recapitulates T-PLL disease progression as shown by immunohistochemistry, flow cytometry and FISH studies (Fig 1). Human tumor cell growth can be monitored in mice peripheral blood using flow cytometry to detect hCD45+ cells.



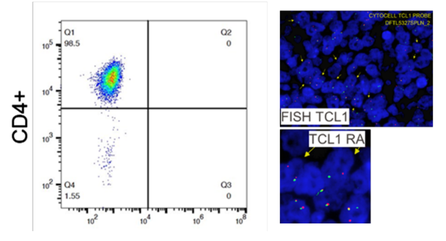


Fig. 1. T-PLL mice model characterization. T-PLL mice model show key characteristics of human T-PLL. Mice develop enlarged spleens. T-PLL cells can be detected in Liver, Spleen and PB. Immunohistochemical and Flow cytometry studies show engrafted T-PLL cells are CD3+ and CD4+. Tumor cells show TCL1 gene rearrangement as detected by FISH.

T-PLL PDX model BH3 profiling

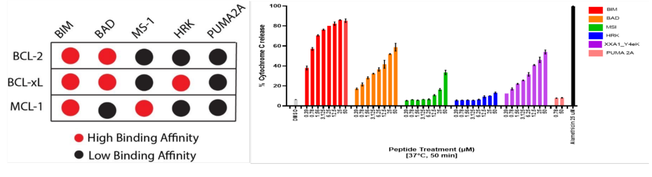


Fig. 2. BH3 Profiling. PDX T-PLL model Splenocytes shows survival dependency on BCL2, MCL1, and BCLxL as seen in T-PLL patient samples.

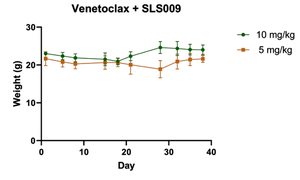


Fig. 3. Weight changes with SLS009 + Venetoclax. Toxicology studies were conducted in mice not bearing T-PLL cells. No adverse effects were observed with the drug combination therapy. There are not significant weight differences between control and treated mice.

Survival Studies

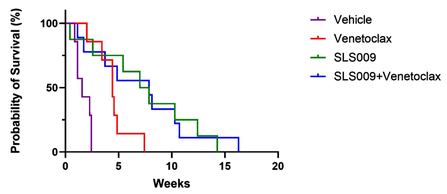
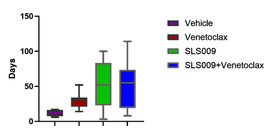


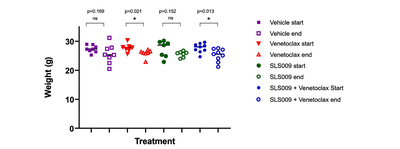
Fig 4. Probability of Survival. Mice treated with SLS009 monotherapy and combination therapy (Venetoclax plus SLS009) had significantly higher survival (7.4 weeks, 7.9 weeks respectively) than Venetoclax alone and Vehicle (4.4 weeks) p<0.05.



	Vehicle	Venetoclax	SLS009	SLS009+Venetoclax
Median survival	1.57143	4.42857	7.42857	7.85714

Fig 5. Survival days per treatment. The arms of SLS009 alone and Venetoclax plus SLS009 had the significantly longer survivals in comparison with Vehicle and Venetoclax alone, p ‹ 0.05

Animal Weight



	Vehicle start	Vehicle end	Venetoclax start	Venetoclax end	SLS009 start	SLS009 end	SLS009 + Venetoclax Start	SLS009 + Venetoclax end
Number of values	8	8	7	7	7	7	9	9
Mean	27.38	25.56	27.81	25.83	27.31	25.56	27.73	25.21
Std. Deviation	1.251	3.308	1.43	1.365	2.868	1.003	1.585	2.156

Fig. 6. Animal weight at the beginning and end of the trial. Animals treated with Venetoclax and Venetoclax + SLS009 have a significant decrease in weight at the end of the treatment compared to the beginning.

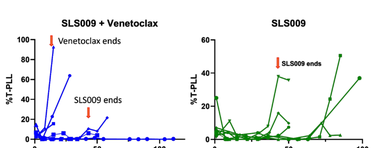


Fig 7. Percentage of hCD45+ cells in PB. SLS009 controlled the number of T-PLL cells in PB better than the other treatments. Mice treated with SLS009 10mg/Kg, have a lower number of circulating T-PLL cells in peripheral blood during the treatment period compared to Vehicle, Venetoclax or Venetoclax + SLS009 alone.

CONCLUSION

- We successfully generated a T-PLL PDX mouse model that has pathological features of T-PLL patients.
- BH3 profiling in PDX T-PLL splenocytes shows survival dependency on BCL2 family.
- 25 mg/Kg Venetoclax (BCL2 inhibitor) and 10 mg/Kg SLS009 (CDK9 inhibitor) combination therapy was well tolerated and maintained low levels of T-PLL cells (hCD45+) cells compared with Venetoclax.
- We demonstrated that the SLS009 monotherapy and combination therapy (Venetoclax plus SLS009) had significantly higher survival (7.4 weeks, 7.9 weeks respectively) than Venetoclax alone (4.4 weeks) p<0.05.
- SLS009 controlled the number of T-PLL cells in PB better than the other treatments.
- T-PLL PDX model will allow us to evaluate the effects of new drugs and new combination therapies for the treatment of this disease.

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