Enhanced antitumor and immune-stimulatory effects of a novel FLT3/AXL inhibitor, SKI-G-801, and anti-PD-1 combination in multiple solid tumors

Ha Ni Jo[1*], Wongeun Lee[3*], Chun-Bong Synn[1,4*], Hee Kyu Lee[5*], Jae-Hwan Kim[1], Do Hee Kim[1,4], Dam Yeon Jeong[1], Jung-Ho Kim[5], Beung-Chul Ahn[1,2], Min Hee Hong[2], Hye Ryun Kim[2], Kyoung-Ho Pyo[1,2#], Byoung Chul Cho[2#]

[1] Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Republic of Korea
[2] Department of Internal Medicine, Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea
[3] JEUK Institute for Cancer Research, Gumi, Republic of Korea
[4] Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea
[5] Oscotec Inc., Seongnam, Republic of Korea

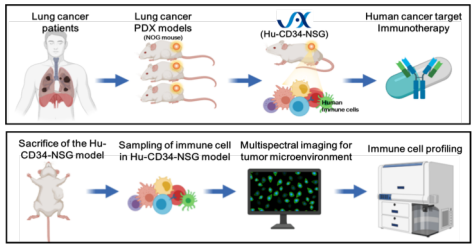
*These authors contributed equally to this work
#These authors contributed equally to this work as corresponding authors

Sponsored by Oscotec Inc.

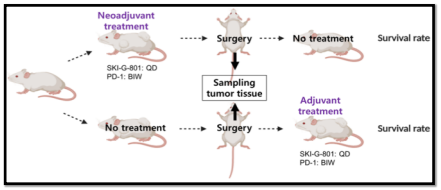
Background

It has previously been shown that SKI-G-801, a novel, selective FLT3/AXL inhibitor, significantly suppressed tumor metastasis and tumor growth by enhancing antitumor immune responses in multiple syngeneic mouse models. In order to substantiate the effect on immune response further, we evaluated SKI-G-801 in combination with pembrolizumab in lung squamous cell carcinoma patient-derived xenograft (PDX) tumors engrafted on Hu-CD34-NSG mice. The advanced model is thought to reflect human immune responses more faithfully and provide a meaningful feedback as to the clinical efficacy. Neoadjuvant therapy refers to systemic drug treatment preceding surgical resection of tumors, in an effort to improve surgical outcome in patients for whom a primary surgical approach is difficult to practice. Given the favorable antitumor immunity elicited by SKI-G-801 in various syngeneic mouse models, we anticipated a synergistic effect with immune checkpoint blockade. Herein, we describe antitumor activity of SKI-G-801 in combination with pembrolizumab on humanized mouse PDX model and 4T1 syngeneic mouse model with neoadjuvant vs adjuvant setting.

Hu-CD34-NSG mouse model design



Neoadjuvant & adjuvant therapy design



Results

Figure 1 The combination effect with SKI-G-801 and aPD-1 in ImmunoAvatars

*YHIM 2004 model represents lung squamous cell carcinoma.

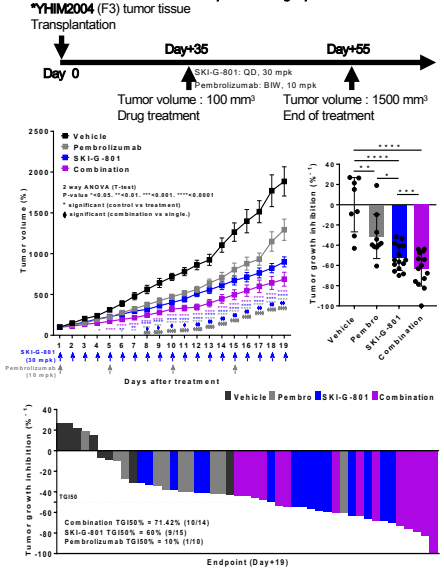


Figure 2 Anti tumor effect with SKI-G-801 by immune response in the immunodeficient NOG mice

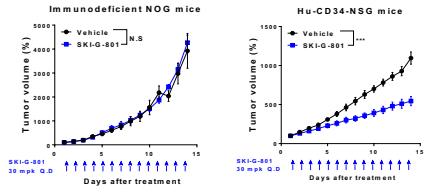


Figure 3 Multispectral imaging of immune microenvironment in ImmunoAvatars

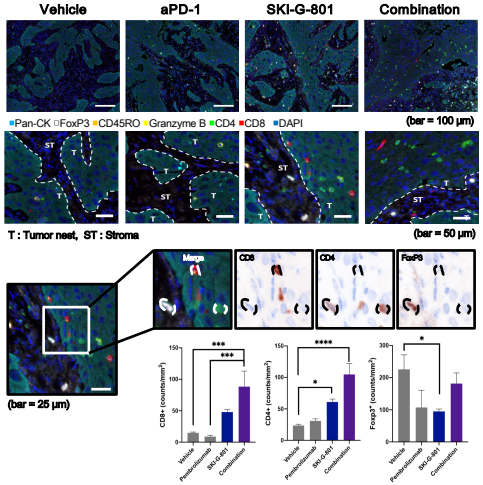
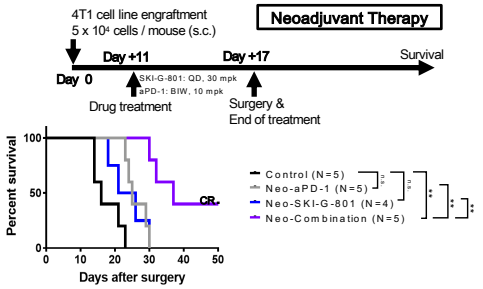


Figure 4 Neoadjuvant combination of aPD-1 and SKI-G-801 treatment most significantly increased survival in 4T1 tumors



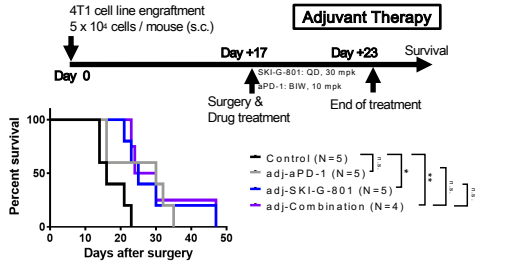
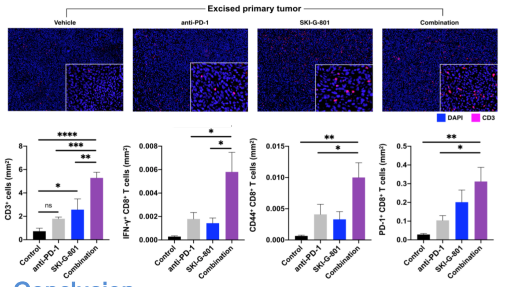


Figure 5 Comprehensive immune profiling from surgically resected 4T1 tumors of neoadjuvant treatment groups



Conclusion

SKI-G-801, a novel FLT3/AXL inhibitor, significantly inhibited the tumor growth by enhancing tumor-infiltrating CD4/CD8+ T cells in TME in lung squamous patient-derived xenograft (PDX) tumor engrafted Hu-CD34-NSG mice. These antitumor activity and immune response were strengthened in combination with pembrolizumab. In contrast, there is no antitumor activity of SKI-G-801 in the immunodeficient NOG mice model. This observation was further confirmed by neoadjuvant therapy model independently. Neoadjuvant combination with SKI-G-801 and anti-PD-1 antibody definitely induced the survival rate longer than aPD-1 alone.

Total CD3⁺, IFN-γ⁺/CD8⁺ (immune reactive T cells), CD44⁺/CD8⁺ (memory T cells) and PD-1⁺/CD8⁺ (tumor specific T cells) T cells in surgically resected 4T1 tumors. Taken together, our results suggest that the inhibition of AXL signal pathway by SKI-G-801 would be efficacious on multiple solid tumors, which would provide a solid rationale for further clinical investigations.

Email: pkhpsh@gmail.com / cbc1971@yuhs.ac