1077 PRECLINICAL AND IND-ENABLING STUDIES OF TXN10128, AN ENPP1 INHIBITOR, FOR CLINICAL EVALUATION IN PATIENTS WITH SOLID TUMOR

[1]Shin-Yeong Kim, [1]Sun Woo Lee, [1]Hye Lim Choi, [1]Jun Yong Choi, [1]Hyang Ji Chae, [1]Eun Kyung Yoo, [1]Chang Won Min, [1]Junghwan Choi, [1]Bo Kyung Sun, [1]Eun Young Kwak, [1]Yongyea Park*, [1]Sungjoon Kim, [2]JongRan Kim, [1]Jong Heun Lee, [1]Chan Sun Park. *[1]Txinno Bioscience Inc., Yongin, Gyunggi-do, Republic of Korea*; *[2]IGNITE clinical development, Anyang, Gyunggi-do, Republic of Korea*

Background An orally available small molecule capable of activating innate immune response can be an ideal drug candidate to enhance clinical benefit of existing immune related therapies in combination. Stimulator of Interferon genes (STING) pathway, a major innate immune pathway, has been known to be down-regulated by ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) enzyme in immune-suppressive tumor microenvironment (TME).[1] Inhibition of ENPP1 can prevent 2'3'-cGAMP degradation in TME and restore STING pathway activation, leading to innate immune activation against tumor. TXN10128, a proprietary ENPP1 inhibitor, has been shown to 1) prevent degradation of 2'3'-cGAMP *in vitro* and *ex vivo*, 2) restore STING pathway activation, 3) have excellent selectivity against related enzymes, 4) inhibit tumor growth together with immune check point inhibitor in mouse model, and 5) have excellent drug-likeness suitable for oral medication.[2] To evaluate the clinical efficacy of TXN10128, further studies are necessary.

Methods *In vivo* efficacies of TXN10128 in monotherapy or in combination with anti-PD-L1 or radiation were evaluated in CT26, MC38, or Pan02 syngeneic model, respectively. Tumor growth was monitored and immune cells in tumor were analyzed by FACS, if applicable. Re-challenge experiment (Pan02 model) were performed with age-matched host animals. Innate immune-related cytokine expression was measured by QPCR assay. GLP toxicology studies were completed in collaboration with Anapath and preclinical PK studies were performed by WuXi AppTec.

Results *In vivo* efficacies of TXN10128 in various settings showed significant tumor growth inhibition (TGI) and synergistic effects in combination. Observed efficacies of TXN10128 were correlated with the innate immune activation leading adaptive immune activation and immune memory. Comparison of cytokine expression showed that delayed induction of IFNB and CXCL10 gene expression and very low induction of TNFA gene expression by TXN10128 compared to STING agonist. *In vitro* and *in vivo* ADME studies showed that excellent exposure in rodent and non-primate animal species and no major concern in metabolic stability, drug-drug interaction and CYP induction. GLP toxicology studies did not find any TXN10128-related toxicological concerns at maximum dose (500 mg/kg, NOAEL (no observed adverse effect level)).

Conclusions Together with significant *in vivo* efficacies in various combination settings and supportive toxicology profile, these studies demonstrated that TXN10128 is a suitable candidate for clinical investigation as a combination partner with existing therapies. Ph I dose escalation study of TXN10128 monotherapy is currently enrolling solid tumor patients in Korea and dose-escalation study of combination therapy will be commencing in near future.

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