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CAN1012: A SELECTIVE AND POTENT TLR7 AGONIST WITH STRONG ANTITUMORAL PROPERTIES MEDIATED BY LOCALIZED INNATE IMMUNE ACTIVATION

¹Henry Yu, ²Hong-Ming Hu*, ¹Rongliang Lou, ¹Wanping Geng, ¹Sanlong Wang, ³William Redmond, ³Yoshinobu Koguchi, ¹Baotian Qin, ⁴John Mao, ⁵Shaoshan Wang. ¹Canwell Pharma Inc, Newton, MA, USA; ²UbiVac, Portland, OR, USA; ³Providence Cancer Institute, Portland, OR, USA; ⁴JWM Pharma, San Francisco, CA, USA; ⁵CanWell Pharma In, Newton, MA, USA

Background Toll-like receptors (TLRs) are commonly expressed on innate immune cells such as macrophages and dendritic cells (DC), and they play crucial roles in 1) mediating the first-line innate immune response against a wide variety of pathogens and 2) promoting adaptive immunity involving T and B cells. The TLR family consists of 10 subtypes (TLR1-TLR10) in humans and 12 (TLR1-TLR9, TLR11-TLR13) in mice. CAN1012 was developed as a selective TLR7 agonist uniquely designed for intratumoral (IT) administration.

Methods CAN1012 was evaluated by *in vitro* cell-based assays and *in vivo* animal models. Its DMPK, safety and toxicology properties were also studied.

Results Based on the receptor screening study, CAN1012 has been proved to have a significant stimulatory effect (NF- κ B activation) via human and mouse TLR7. In addition, CAN1012 stimulated significant IFN- α release from human PBMC at low concentrations (nM), whereas TNF- α secretion required a relatively high concentration.

Most importantly, CAN1012 induced a robust production of IFN- α exclusively by plasmacytoid DCs in human PBMC. When given intratumorally, CAN1012 exposure in tumor tissues was over 1,000-fold higher than in blood, resulting in much less systemic toxicity. The antitumoral effects of IT-administered CAN1012 monotherapy or combined with other therapeutic agents were investigated in mouse SCC7, CT26, and MC38 syngeneic tumor models. The results showed that CAN1012 possessed significant anti-tumor growth effects in a dose-dependent and schedule-dependent manner, and antitumoral effects could be augmented when combined with other agents. Pharmacodynamic studies revealed that IT administration of CAN1012 increased CD4+ and CD8+ T cell infiltration but decreased the number of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) in the tumor microenvironment (TME). CAN1012 has a favorable ADME/PK profile when administered subcutaneously in mice, rats and monkeys, and its pharmaceutical properties have also been optimized for IT administration.

Conclusions In conclusion, CAN1012 is a potent, safe, and selective TLR7 agonist and could be a best-in-class agent for cancer immunotherapy. A first-in-human Phase I clinical study in advanced cancer patients is ongoing in the US (NCT04987112).

Trial Registration NCT04987112

Ethics Approval Aniaml studies had been approved by the ethics review committee at the institution at which the studies were conducted

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