HBW-008-A, a Novel, Potent, Selective, Safe and Bioavailable p21-Activated Kinase 4 (PAK4) Inhibitor, is an Efficacious Adjuvant Agent for PD-1 Therapy in Mice

Ning Lee,¹ Yingfu Li,¹ Guanfeng Liu,¹ and Mao Yang¹

¹Chengdu Hyperway Pharmaceuticals

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PAK4, a member of the serine-threonine PAK kinase family involved in a wide range of cellular functions, is often dysregulated across diverse cancer types. PAK4 may promote cancer progression, through altering biological capabilities such as proliferation, epithelial-mesenchymal transition (EMT), invasion, metastasis and tumor microenvironment conditioning. Lately, it has been shown that a PAK4 inhibitor (PAK4i) may enhance the efficacy of PD-1 blockade and CAR-T cells, and provide a novel adjuvant agent for the current immunotherapy, a prime-time cancer treatment yet struggled with low response rate. Furthermore, a PAK4i may sensitize cancer cells to chemotherapy and radiotherapy. With over 20 years in development, many PAK4is have been published but only few entered clinical, and none is approved by far. issues of existing compounds include unfavorable pharmacokinetic (PK) profiles and the lack of selectivity due to high homology among PAK family members. Through our medicinal chemistry efforts, we have discovered a novel orally bioavailable small-molecule PAK4i, HBW-008-A, that has a superior PAK4 inhibition and selectivity against PAK2 (cardiovascular liability) as compared with other known PAK4is. In a mouse MC38 colon cancer model, as combined with mPD-1, HBW-008-A demonstrated an enhanced anti-tumor efficacy than mPD-1 mono therapy, without any toxicity issue. HBW-008-A exhibited a good hepatic microsomal stability, as well as plasma stability in several animal species including human. In a head-to-head rat PK study, HBW-008-A displayed comparable exposures to the pan-PAK inhibitor PF-3758309. In addition, HBW-008-A had higher exposures in liver, lung, kidney, intestine, stomach, and pancreas than those in blood. In a 14-day toxicity study in rats using doses up to 300 mg/kg, HBW-008-A showed no sign of safety concern. Taken together, we have demonstrated that HBW-008-A is a validated candidate for future clinical studies in cancer patients.

SIGNIFICANCE STATEMENT The novel orally bioavailable small-molecule PAK4i, HBW-008-A, produced an enhanced anti-tumor efficacy as combined with mPD-1 in a mouse MC38 colon cancer model. HBW-008-A also presented a better safety and PK profile than other known PAK4is. These preclinical studies have established HBW-008-A a more advantageous PAK4i to be tested clinically as a potential adjuvant agent for immunotherapy in treating cancers.

All authors are employees of Chengdu Hyperway Pharmaceuticals.