Phase 1 First in man Trial of Novel ACK1 Inhibitor (R)-9b in Patients with Prostate Cancer

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Background Prostate cancer (PC) is one of the leading cause of cancer deaths among American men. Advanced PC patients often receive androgen deprivation therapy, but, the recalcitrant disease recurs within 2-3 years, referred to as the Castration Resistant Prostate Cancer (CRPC). Androgen Receptor (AR) antagonists such as enzalutamide (Enz) or abiraterone (Abi) are currently favored therapeutics for PC patients, however, virtually all patients develop resistance. Post-CRPC state, therapeutic options for the recurrent disease are limited.

Methods We discovered a non-receptor tyrosine kinase, ACK1, as a novel epigenetic modifier in prostate tumors, regulating AR/AR-V7 expression. Enthused with these data, we developed a new class of ACK1 small molecule kinase inhibitor, (R)-9b.

Results (R)-9b inhibits ACK1 and downregulates AR and prostate specific antigen (PSA) expression to suppress prostate xenograft tumor growth. Moreover, in immune competent mouse models, (R)-9b induces significant CD4+ and CD8+ T cell activation against syngeneic prostate tumors. Employing ex vivo 3-D assays, we confirmed that (R)-9b functionally reinvigorates peripheral blood mononuclear cells (PBMCs) of the CRPC patients to mount a robust immune response against human CRPC organoids. Together, these data indicated that ACK1 inhibitor, (R)-9b with tumor-intrinsic and tumor-extrinsic activities in the host tumor microenvironments is a novel class of inhibitor with much needed immunomodulatory activity. Prolonged (R)-9b treatment exhibited normal histology suggesting that it is not associated with toxicity, further underscoring the importance of targeting ACK1 to overcome resistance to AR-targeted therapies.

Conclusions We have completed extensive pre-Investigational New Drug (IND) studies, which revealed that (R)-9b possessed excellent drug-like properties. IND have been obtained from FDA (IND#167907). The phase I clinical trial for ACK1 inhibitor (R)-9b in CRPC patients to examine its ability to overcome CRPC resistance by cytotoxic and immunomodulatory activity started in September, 2025. (Clinicaltrials.gov/study/**NCT06705686**; acronym: PHAROS).

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Conflicts of Interest Disclosure Statement. Patents `Inhibitors of ACK1/TNK2 Tyrosine Kinase', (patent no. 9,850,216 and 10,017,478) covers (R)-9b molecule. N.P.M. and K.M are named as inventor of these patents. Both the patents have been licensed by TechnoGenesys, Inc., N.P.M. and K.M are co-founders of TechnoGenesys, Inc., own stocks, and serve as consultants.