SYSTEMIC DELIVERY OF NOVEL, ALLOSTERIC STING AGONIST CRD3874-SI LEADS TO ROBUST ANTI-CANCER ACTIVITY BY GENERATING PRO-INFLAMMATORY TYPE I IFN SIGNALS WHILE BLOCKING PROTON CHANNEL MEDIATED TOXICITY


1Curadev, Noida, UP, India; 2Curadev, Sandwich, Kent, UK; 3genOway, Lyon, France; 4MSKCC, New York, NY, USA

Background STING activates Type1 interferon and pro-inflammatory responses to drive anti-tumor immunity. Current STING agonists under clinical investigation show limited efficacy due to safety considerations that prevent systemic administration. CRD3874-SI, a novel allosteric systemically safe small molecule STING agonist, addresses these shortcomings by blocking STING’s proton channel activity associated with runaway inflammation.

Methods Anti-cancer activity of CRD3874-SI by the IV route was evaluated in human STING KI C57/BL6 mice (Genoway) in various murine tumor models. PBMCs were used to measure cytokine levels and THP1 cells were used for the measurement of autophagy and inflammasome markers.

Results Intravenous administration of CRD3874-SI in human STING knock-in mice caused tumor regression in several cold tumor models such as B16F10, PAN02, LL2, C1498. The compound was well tolerated at high doses in the primate GLP study when administered intravenously and caused dose and exposure dependent increases in CXCL10. This profile of retaining the high efficacy of a STING agonist while demonstrating systemic safety is unique to CRD3874-SI. The mechanism for this unusually high safety margin may be attributed to CRD3874’s ability to block STING’s proton channel activity and prevent the release of inflammasome promoting cytokines such as IL1.

Conclusions The ability of CRD3874-SI to generate impressive anti-tumor immune responses in cold tumors as a single agent coupled with its excellent IV safety profile in non-human primates make it a differentiated next generation STING agonist. An investigator sponsored FIH Phase 1 trial with CRD3874-SI has been initiated at Memorial Sloan Kettering, NY, in sarcoma, MCC patients under the supervision of Dr. Ciara Kelly (NCT06021626).

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