R. Shrivastava: A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **M. Banerjee:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **D. Pryde:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd, UK. **S. Middya:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **S. Debnath:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **A. Middya:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **D. Yadav:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **N. Mane:** A. Employment (full or part-time); Significant; Curadev Pharma Pvt. Ltd. **N. Rawat:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **R. Ghosh:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **A. Gautam:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **M. Padaliya:** A. Employment (full or part-time); Modest; Curadev pharma pvt ltd. **S. Bano:** A. Employment (full or part-time); Modest; Curadev pharma pvt ltd. **S. Basu:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. **A. Surya:** A. Employment (full or part-time); Significant; Curadev pharma pvt ltd. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Curadev pharma pvt ltd.

P01.09 CRD3874-SI: A NOVEL ALLOSTERIC STING AGONIST WITH HIGH SYSTEMIC TOLERABILITY

[1]SK Middya*, [1]M Banerjee, [1]R Shrivastava, [1]A Middya, [1]N Mane, [1]N Rawat, [1]T Soram, [1]D Chakraborty, [1]R Ghosh, [1]R Mansuri, [1]D Yadav, [1]A Gautam, [1]K Puniya, [2]D Pryde, [1]S Basu, [3]F Sônego, [3]G Martin, [3]K Thiam, [4]C Kelly, [1]A Surya. *[1]Curadev Pharma, Noida, India*; *[2]Curadev Pharma, Sandwich, UK*; *[3]genOway, Lyon, France*; *[4]Memorial Sloan Kettering Cancer Center, New York, NY, USA*

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Background STING activation by natural and targeted competitive ligands leads to the generation of Type I interferons as well as pyroptosis and autophagy of the cells expressing STING causing runaway inflammation. This overt inflammation is due to STING's newly discovered proton channel activity. STING agonists tested in the clinic thus far have shown limited systemic tolerability and also a tendency to kill the very immune cells that they are designed to activate. CRD3874 is a novel allosteric small-molecule human STING agonist with a unique binding mode that activates canonical STING pathway while simultaneously blocking STINGs proton transport activity that is associated with pyroptosis and autophagy.

Materials and Methods Allosteric binding was established using radioligand binding assays. Anti-cancer activity was established in human STING KI C57/BL6 mice (genOway, France). Inflammasome and autophagy markers were studied in human and mouse cells. Safety studies was evaluated in cynomolgus monkeys.

Results As opposed to competitive STING agonists, CRD3874 potentiates the binding of radiolabeled cGAMP to STING. CRD3874, like other STING agonists, led to dose dependent increase in Type1 interferons and other pro-inflammatory cytokines from immune cells. In contrast to other STING agonists, activation of STING by CRD3874 did not lead to induction of autophagy or Inflammasome markers in cells or mice. Intravenous administration of CRD3874-SI in human STING knock-in mice caused potent anti-tumor effect and survival benefit in multiple murine tumor models. Intravenous infusion of the compound was well tolerated at high doses in the primate GLP study and caused exposure dependent increases in cytokines. This profile of retaining the high efficacy of a STING agonist while demonstrating systemic safety is unique to CRD3874-SI.

Conclusions CRD3874-SI is a systemically administered novel allosteric STING agonist with promising single agent activity and an excellent IV safety profile. 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).

S.K. Middya: A. Employment (full or part-time); Significant; Curadev Pharma. **M. Banerjee:** A. Employment (full or part-time); Significant; Curadev Pharma. **R. Shrivastava:** A. Employment (full or part-time); Significant; Curadev Pharma. **A. Middya:** A. Employment (full or part-time); Significant; Curadev Pharma. **N. Mane:** A. Employment (full or part-time); Significant; Curadev Pharma. **N. Rawat:** A. Employment (full or part-time); Significant; Curadev Pharma. **T. Soram:** A. Employment (full or part-time); Significant; Curadev Pharma. **D. Chakraborty:** A. Employment (full or part-time); Significant; Curadev Pharma. **R. Ghosh:** A. Employment (full or part-time); Significant; Curadev Pharma. **R. Mansuri:** A. Employment (full or part-time); Significant; Curadev Pharma. **D. Yadav:** A. Employment (full or part-time); Significant; Curadev Pharma. **A. Gautam:** A. Employment (full or part-time); Significant; Curadev Pharma. **K. Puniya:** A. Employment (full or part-time); Significant; Curadev Pharma. **D. Pryde:** A. Employment (full or part-time); Significant; Curadev Pharma. **S. Basu:** A. Employment (full or part-time); Significant; Curadev Pharma. **F. Sônego:** A. Employment (full or part-time); Significant; genOway. **G. Martin:** A. Employment (full or part-time); Significant; genOway. **K. Thiam:** A. Employment (full or part-time); Significant; genOway. **C. Kelly:** A. Employment (full or part-time); Significant; Memorial Sloan Kettering Cancer Center. **A. Surya:** A. Employment (full or part-time); Significant; Curadev Pharma. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Curadev Pharma.

P01.10 REAL-TIME INTERACTION CYTOMETRY REVEALS DIFFERENT BINDING KINETICS OF ANTIBODIES TARGETING MEMBRANE PROTEINS ON FIXED VERSUS LIVING CELLS

V Hafner, A Marszal, U Rant, N Matscheko. *Dynamic Biosensors GmH, München, Germany*

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Background The field of therapeutic antibody developmenthas witnessed significant growth since the introduction of the first-therapeutic monoclonal anti-CD3 antibody, Muronomab, in 1986 [1].Numerous investigations indicate that the dissociation rate of antibodies playsa predictive role in their clinical effectiveness [2, 3]. Therefore, it isimperative to conduct kinetic rate analyses to enhance the efficacy and safetyof these therapeutic agents. Transmembrane proteins such as PD-(L)1, CD3 orHER2 represent the most common targets. Their binding kinetics are influencedby neighbouring coreceptors as well as by their density and mobility within themembrane. Preserving these target molecules within their native cell membrane