SYNB1891, A BACTERIUM ENGINEERED TO PRODUCE A STING AGONIST, DEMONSTRATES TARGET ENGAGEMENT IN HUMANS FOLLOWING INTRATUMORAL INJECTION

¹Richard Riese, ²Jason Luke*, ³Karl Lewis, ⁴Filip Janku, ⁴Sarina Piha-Paul, ⁵Claire Verschraegen, ¹Aoife Brennan, ⁶Michael Armstrong, ⁷Mary Varterasian, ¹Anna Sokolovska, ⁸James Strauss. ¹Synlogic Inc, Cambridge, MA, USA; ²UPMC Hillman Cancer Center, Pittsburgh, PA, USA; ³University of Colorado, Aurora, CO, USA; ⁴University of Texas, Houston, TX, USA; ⁵Ohio State University, Columbus, OH, USA; ⁶QVIA Biotech, Durham, NC, USA; ⁷Ann Arbor Drug Safety, LLC, Ann Arbor, MI, USA; ⁸Mary Crowley Cancer Research, Dallas, TX, USA

Background SYNB1891 is a live, modified strain of probiotic *E. coli* Nissle engineered to produce cyclic dinucleotides under hypoxia leading to stimulator of interferon genes (STING)-activation in phagocytic antigen-presenting cells in tumors and activating complementary innate immune pathways.

Methods This first-in-human study (NCT04167137) enrolled patients with refractory advanced solid tumors to receive intratumoral (IT) injections of SYNB1891 monotherapy or in combination atezolizumab. Patients enrolled in the monotherapy arms received doses of 1×10^6 - 3×10^8 live cells on Days 1, 8 and 15 of the first 21-day cycle and then on Day 1 of each subsequent cycle. Patients enrolled in the 2 combination cohorts received doses of 1×10^7 - 3×10^7 live cells in combination with atezolizumab administered on a 21-day cycle. The primary objective of the study was to evaluate safety and tolerability of SYNB1891 alone and in combination with atezolizumab. Other objectives include SYNB1891 kinetics in blood and injected tumor, STING-target engagement as assessed by IT gene expression and serum cytokines, and tumor responses.

Results This interim analysis includes 23 patients across 6 monotherapy cohorts dosed at 1×10^6 , 3×10^6 , 1×10^7 , or 3×10^7 , 1×10^8 and 3×10^8 live cells, and 7 patients dosed in 2 combination therapy cohorts (1×10^7 and 3×10^7 live cells). The mean (range) age was 61 (25–82); 19 patients were female. There were 4 cytokine release syndrome events in monotherapy cohorts, including one grade 3 event which met the criterion for dose limiting toxicity at 3×10^8 live cells; there were no other SYNB1891-related serious adverse events. There were no SYNB1891-related infections. SYNB1891 was not detected in the blood at 6 or 24 hours after the first dose or intratumorally 7 days following the first dose. Treatment with SYNB1891 demonstrated activation of the STING pathway and target engagement as assessed by upregulation of interferon-stimulated genes (ISG15, IFIT1, IFI2), chemokines/cytokines (CXCL9, CXCL10, TNFRS18, TNFSF10) and T-cell response genes (GZMA, CD4, PD-L2) in core biopsies obtained pre-dose and 7 days following the third weekly dose. In addition, there was a dose-response increase in serum cytokines. Durable, stable disease was observed in two patients treated with SYNB1891 monotherapy refractory to prior PD-1/L1 antibodies with vulvar melanoma (1×10^6 live cells; RECIST -28%) and small cell lung cancer (1×10^7 live cells; RECIST -12%).

Conclusions Repeat IT injection of SYNB1891 as monotherapy and in combination atezolizumab in this ongoing study is safe and well-tolerated up to at least 1×10^8 live cells, and shows evidence of STING pathway target engagement.

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Trial Registration clinicaltrials.gov (NCT04167137)

Ethics Approval The study protocol, the informed consent form (ICF), and printed subject information materials were

reviewed and approved by the institutional review board (IRB) at the investigational site before any study procedures were performed. Written informed consent to participate in the study was obtained from each subject before any study-specific procedures were performed. The Ohio State University Cancer Institutional Review Board; Approval ID: 2020C0194MD Anderson Cancer Center Institutional Review Board; Approval ID: 2019-0576 Mary Crowley Medical Research Center Institutional Review Board; Approval ID: 19-31 SYNB1891-CP-001 North Texas Institutional Review Board; Approval ID: 2019.040 WIRB Approval ID: 20192779 University of Pittsburgh Institutional Review Board Approval ID: STUDY20010116

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