SYNB1891, a bacterium engineered to produce a STING agonist, demonstrates target engagement in humans following intratumoral injection

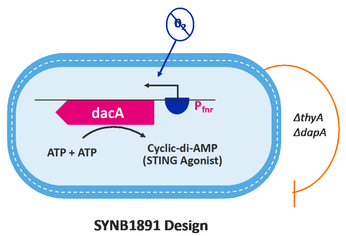
Janku F, MD Anderson Cancer Center; Piha-Paul SA, MD Anderson Cancer Center; Luke JJ, UPMC Hillman Cancer Center; Lewis KD, University of Colorado School of Medicine; Verschraegen CF, Ohio State University College of Medicine; Brennan AM, Synlogic; Riese RJ, Synlogic; Armstrong MB, IQVIA Biotech; Varterasian M, Pharmaceutical Consultant; Sokolovska A, Synlogic; Strauss J, Mary Crowley Cancer Research

Abstract

SYNB1891 is a live, modified strain of the 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. This first-in-human study (NCT04167137) enrolled patients with refractory advanced solid tumors or lymphoma to receive an intratumoral (IT) injection of SYNB1891 either alone or in combination atezolizumab. Patients enrolled in the monotherapy arms received doses of $1x10^6$ - $3x10^8$ 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 does of $1x10^7$ - $3x10^7$ live cells with atezolizumab administered on a 21-day cycle. The primary objective of the study was to evaluate the safety and tolerability of SYNB1891 given alone and in combination of atezolizumab. Other objectives include SYNB1891 kinetics in blood and the injected tumor, STING-target engagement as assessed by IT gene expression and serum cytokines, and tumor responses. This interim analysis includes 24 patients across 6 monotherapy cohorts dosed at $1x10^6$, $3x10^6$, $1x10^7$, or $3x10^7$, $1x10^8$ and $3x10^8$ live cells, and 8 patients dosed in 2 combination therapy cohorts ($1x10^7$ and $3x10^7$ live cells). The mean (range) age was 60 (25-82); 20 patients were female. There were 5 cytokine release syndrome events in the monotherapy cohorts, including one which met the criterion for dose limiting toxicity at the $3x10^8$ 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, IFIt2), 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 3 patients refractory to prior PD-1/L1 antibodies with vulvar melanoma ($1x10^6$ live cells), basal cell carcinoma ($3x10^6$ live cells) and small cell lung cancer ($1x10^7$ live cells). Repeat IT injection of SYNB1891 as monotherapy and in combination atezolizumab in this ongoing study is safe and well-tolerated up to at least $1x10^8$ live cells, and shows evidence of STING pathway target engagement.

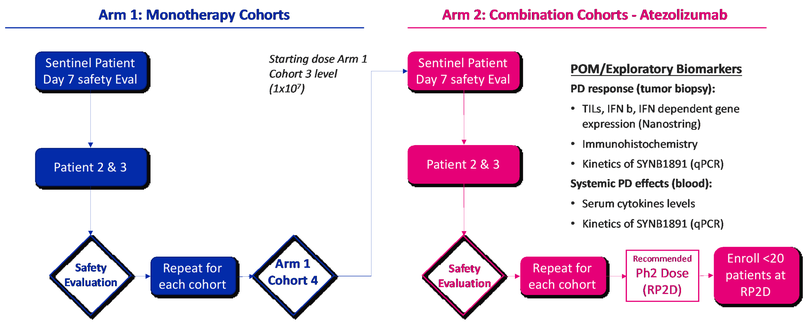
SYNB1819 Strain Design

Attribute	Benefit
STING agonist	Innate immune activator to induce interferon responses and drive T cell priming and recruitment
Bacterial chassis	Chassis effects drive immune responses relevant to multiple therapeutic targets
IT delivery	Targeted delivery to antigen presenting cells in the TME
Pathfinder	Feasibility and safety data establish path for combinations and future programs



SYNB1891 Design

Study Design



Clinical Summary

- A total of 32 patients received SYNB1891 across 5 sites in the US
  - 24 patients in Arm 1 (monotherapy) were treated on 6 dose cohorts, 1×10^6 (n = 3), 3×10^6 (n = 3), 1×10^7 (n = 4), 3×10^7 (n = 5), 1×10^8 (n = 3), and 3×10^8 (n = 6) live cells
  - 8 patients in Arm 2 (combination therapy with standard dose of atezolizumab) were treated on 2 dose cohorts, 1×10^7 (n = 4) and 3×10^7 (n = 4) live cells
  - 1 patient (Arm 2) remains on treatment and 31 patients have discontinued from the study
- Demographics
  - Most (29 patients, 91%) of the 32 patients were Caucasian, and 3 patients (9%) were Black, with more females (20 patients, 63%) than males (12 patients, 38%) and more patients in the < 65 years age category (21 patients, 66%) than ≥ 65 years category (11 patients, 34%).
  - Tumor types include: Basal cell carcinoma (1), colorectal cancer (1), endometrial cancer (1), esophageal cancer (3), liposarcoma (1), melanoma (7), merkel cell carcinoma (1), NSCLC (1), Other (12), sarcoma (1), SCLC (1), squamous cell carcinoma of skin (1), testicular cancer (1)
- As of 23 August 2021, 153 doses of SYNB1891 (Arms 1 and 2) and 17 doses of atezolizumab (Arm 2) had been administered
- Three subjects had durable, stable disease after treatment with SYNB1891: 100-002 vulvar melanoma (228 days; $1x10^6$ live cells), 600-002 small cell lung cancer (>342 days; $1x10^7$ live cells) and 100-004 basal cell carcinoma (83 days; $3x10^6$ live cells)

Safety Summary (as of 11AUG21)

- Fourteen patients (44%) experienced TEASs related to SYNB1891. In Arm 2, no AEs were assessed as related to atezolizumab treatment. Four patients (13%) experienced serious adverse events (SAEs) that were considered related to SYNB1891 treatment, all of which were events of CRS.
- Cytokine release syndrome: Five patients (16%), all in Arm 1, experienced CRS with 2 patients experiencing CRS after the first dose of SYNB1891 and 3 patients after the second dose. One CRS event, occurring at the dose of $3x10^8$ live cells, was assessed as grade 3, was associated with respiratory failure and met the criteria for DLT. Three of the 5 patients were successfully able to continue treatment; 1 patient came off study due to CRS and another patient stopped treatment for an unrelated reason.
- Injection site reaction: Four patients (13%) experienced injection site reactions. These reactions were variably treated with supportive medications and prophylactic medications on subsequent cycles. Injection site reactions did not prohibit further dosing with SYNB1891.
- Systemic infection – No systemic infections were considered related to SYNB1891.
- Dose-limiting toxicity was observed for 1 patient (grade 3 CRS) at the highest administered dose level in Arm 1 (3×10^8 live cells); no DLTs were observed in Arm 2. No MTD/RP2D was determined for either Arm 1 or Arm 2 prior to the study being terminated. The maximum administered doses of SYNB1891 were deemed safe in both arms.

Dose related increases in serum cytokine levels

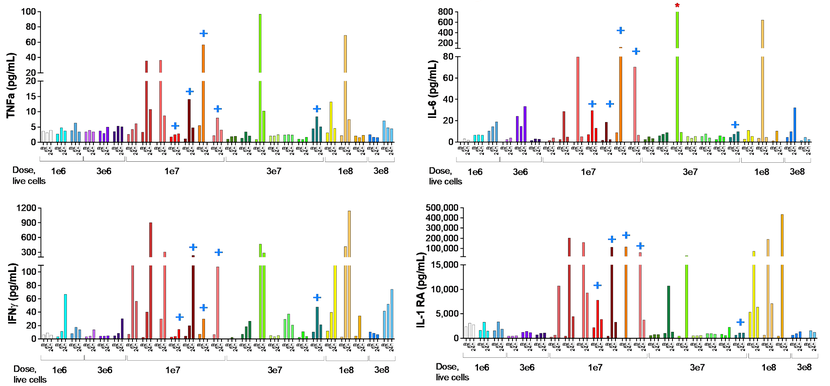


Fig 1. Serum cytokines were measured at baseline (pre-dose), 6h after injection and 24h after injection with different doses of SYNB1891. Each color denotes a separate patient. Data marked with a + were from the combination cohort (Arm 2).

Evidence of STING target engagement

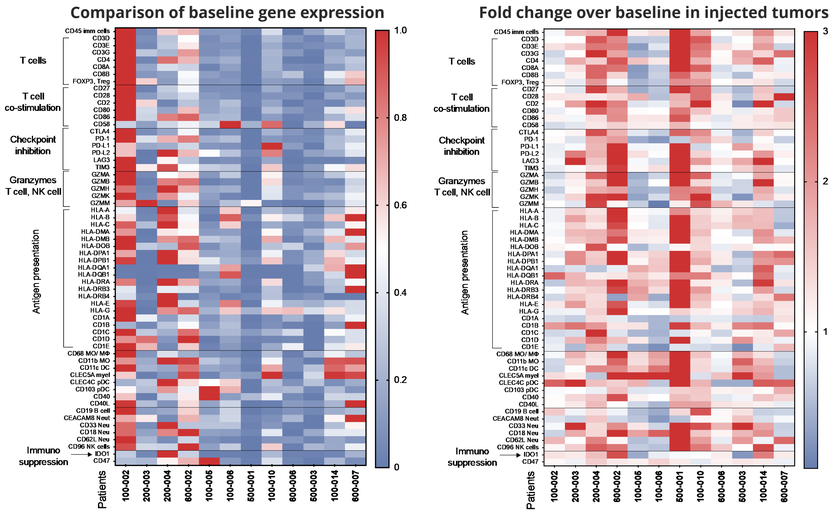


Fig 2. (Left). Baseline gene expression levels across different tumor types. Data were normalized to the highest and lowest expressed gene in each row. The majority of injected tumors had low levels of inflammatory gene expression. (Right) Fold change in gene expression over baseline in injected tumors. Fold changes in gene expression after 1 cycle of SYNB1819 treatment relative to baseline samples as determined by Nanostring. Data were available for the following tumor types (live cell dose): 100-002 Vulvar melanoma (1e6), 200-003 Liposarcoma (1e6), 200-004 Sarcoma (left chest, breast; 3e6), 600-002 SCLC (1e7), 100-005 Chondrosarcoma (1e7), 100-006 Cutaneous squamous cell carcinoma (1e7), 500-001 Melanoma (3e7), 100-010 Oropharynx Squamous Cell Carcinoma (1e8), 600-006 Melanoma (1e8), 500-003 Melanoma (3e8), 100-014 Metastatic adenocarcinoma of jejunum (1e7 + aPD1), 600-007 Esophageal cancer (1e7 + aPD1). Subjects 100-002 and 600-002 had durable, stable disease.

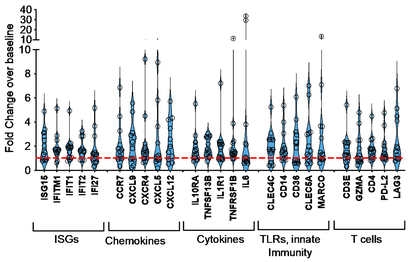


Fig 3. Change from baseline in gene expression for the 5 most upregulated genes across 5 different gene categories. Data are shown for the same 12 patients depicted in Fig. 2. Each symbol depicts the data for a single patient.
ISG = interferon stimulated genes.

Conclusions

- Repeat IT injection of SYNB1891 is safe and well-tolerated in a heterogenous population up to a dose of $3x10^8$ live cells.
  - No infections related to SYNB1819 were seen
- SYNB1819 demonstrates target engagement as assessed by increases in serum cytokines and upregulation of interferon stimulated genes (ISGs)
- Evidence of durable stable disease was seen in 3 patients, and was associated with upregulation of genes tied to immune activation lymphocytes in 2 of the subjects
  - Gene expression data was not available for the third subject with durable, stable disease