Intratumoral injection of SYNB1891

A Synthetic Biotic medicine designed to activate the innate immune system. Therapy demonstrates target engagement in humans including intratumoral STING activation.

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Introduction and Methods

SYNB1891 Strain

- Live, modified strain of the probiotic E. coli Nissle engineered to produce cyclic dinucleotides (CDN) under hypoxia leading to stimulator of interferon genes (STING)-activation
- Preferentially taken up by phagocytic antigen-presenting cells in tumors, activating complementary innate immune pathways (direct CDN STING activation; cGAS-mediated STING activation and TLR4/MyD88 activation by the bacterial chassis)

Phase 1 First-in-Human Clinical Trial

- Enrolling patients with refractory advanced solid tumors or lymphoma
- Intratumoral (IT) injection of SYNB1891 on Days 1, 8 and 15 of the first 21-day cycle and then on Day 1 of each subsequent cycle.
- Dose escalation planned across 7 cohorts ($1x10^6$ – $1x10^9$ live cells) with Arm 1 consisting of SYNB1891 as monotherapy, and Arm 2 in combination with atezolizumab

SYNB1891 was safe and well-tolerated in heterogenous population

Nov 2020: Interim Analysis

Focused on first 11 monotherapy pts dosed at 1e6 to 3e7 live cells

Mean age 56 yo; 82% female; 82% white; all patients progressed on prior oncology therapies

IA Updated through 15 Mar 2021

No DLTs | No additional CRSs | No additional SYNB1891-related SAEs

15 Mar 2021: Current Enrollment:

22 patients across 4 sites in the US

Monotherapy dosed at 1e6 to 1e8 live cells; combination therapy dosed at 1e7 live cells

Tumor types: melanoma [4], sarcoma [4], esophageal [4], squamous (including 2 head and neck) [4], colon/colorectal [2]; small cell lung, basal cell, bile duct adeno, jejunum adeno

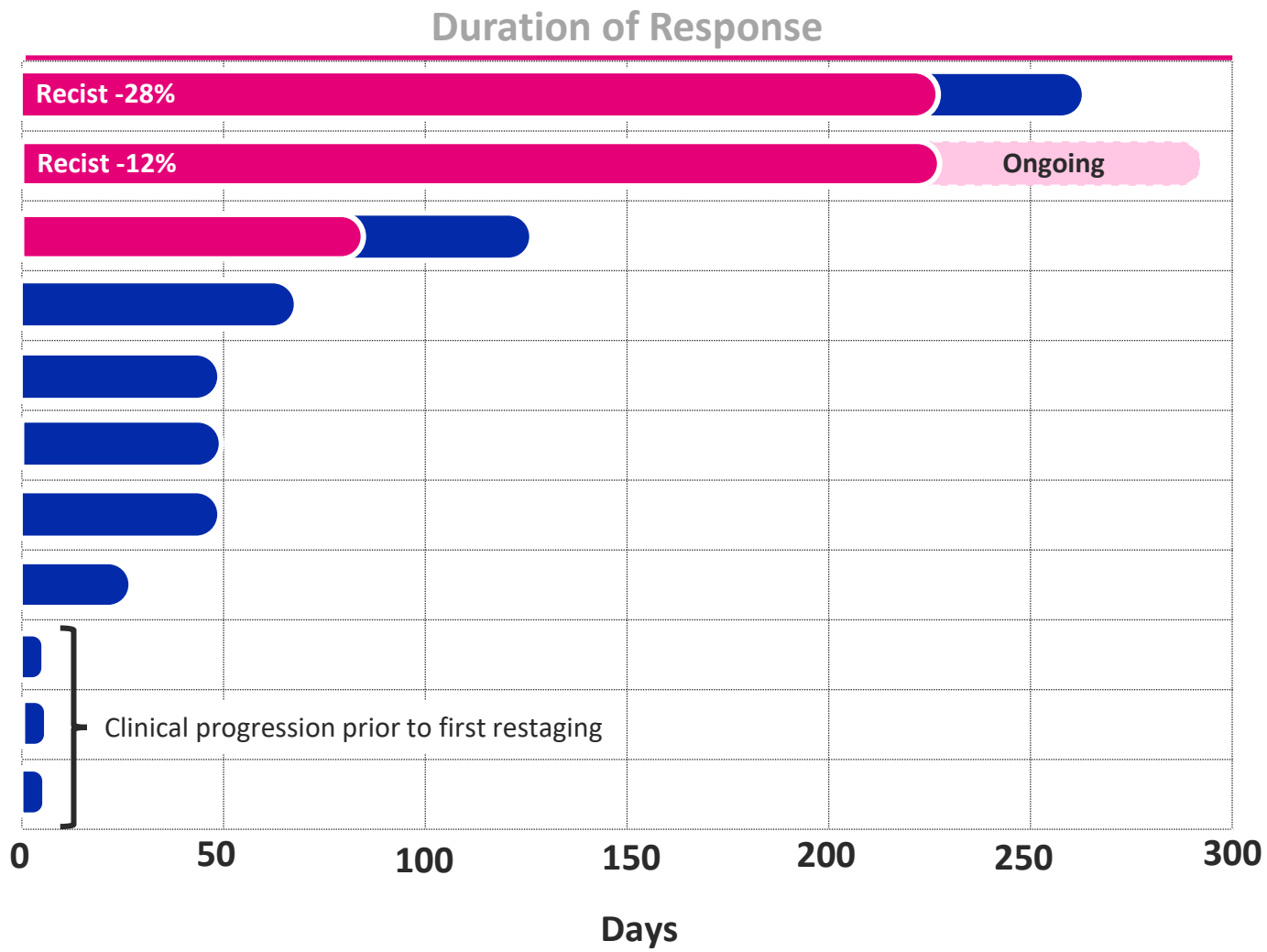
59 IT Doses Administered

- ✓ No Dose limiting toxicities
- ✓ No SYNB1891-related infections
- ✓ No discontinuations due to adverse events (AEs)

- Two events of cytokine release syndrome – both resolved within 1 day
- 1 injection site reaction/erythema (mod)
- No bacteria DNA detected by blood PCR 6 hours after the 1st dose at any dose

2 out of 11 patients with stable disease

Patient	Dose	Tumor
100-002	1e6	Vulvar melanoma
600-002	1e7	Small Cell Lung
100-004	3e6	Basal Cell
100-006	1e7	Squamous Cell
100-005	1e7	Bone chondrosarcoma
200-003	1e6	Liposarcoma
200-004	3e6	Sarcoma - breast
600-003	1e7	Bile duct adeno
200-001	1e6	Synovial Sarcoma
600-001	3e6	Esophageal
600-004	3e7	Vulvar squamous cell



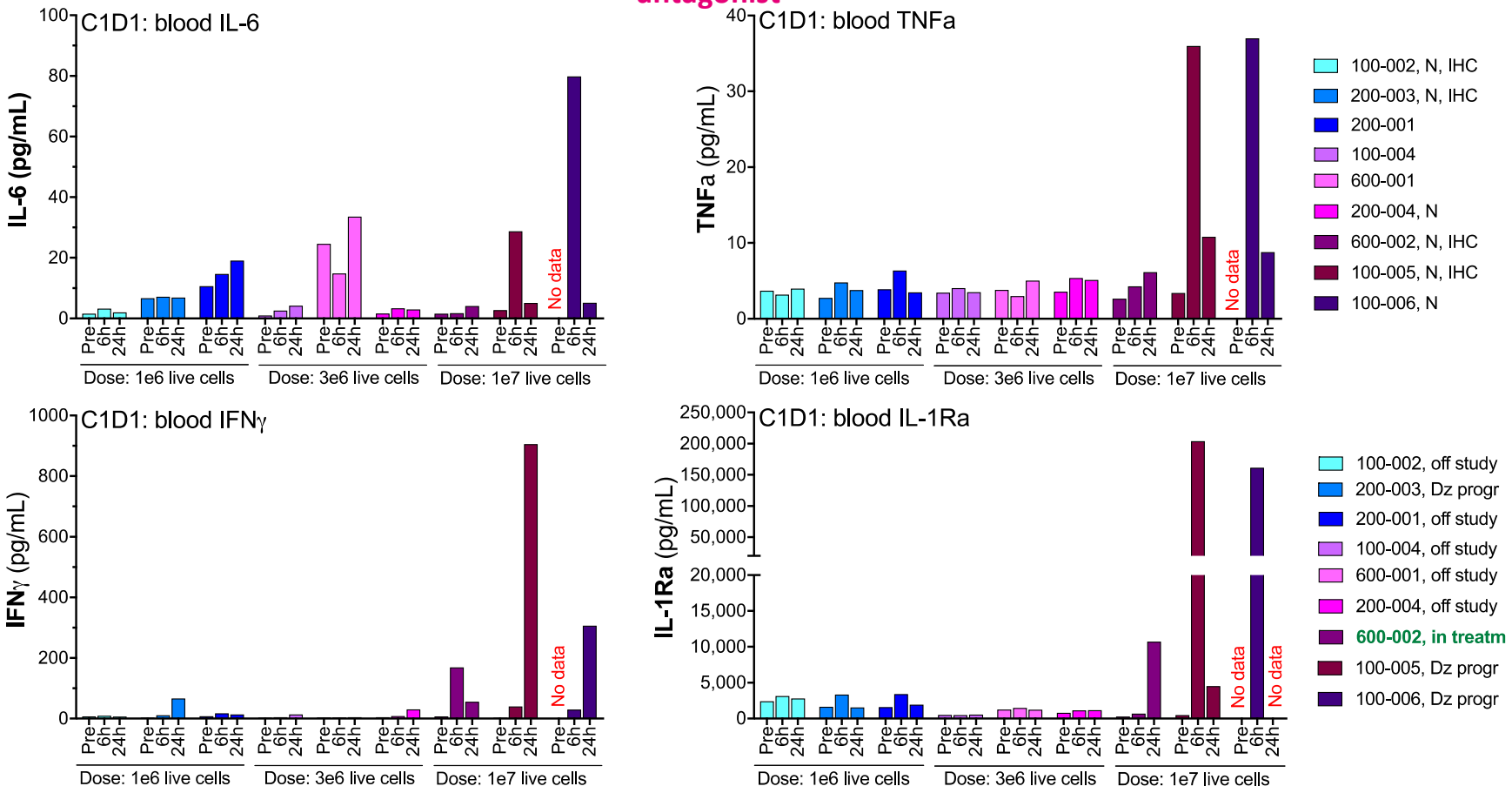
Serum cytokines suggest systemic inflammatory response with dose escalation

Serum Cytokines:

(Baseline, 6 and 24h post-dose): IL-6, TNFα, IFNγ IL-1R antagonist

Pro-inflammatory

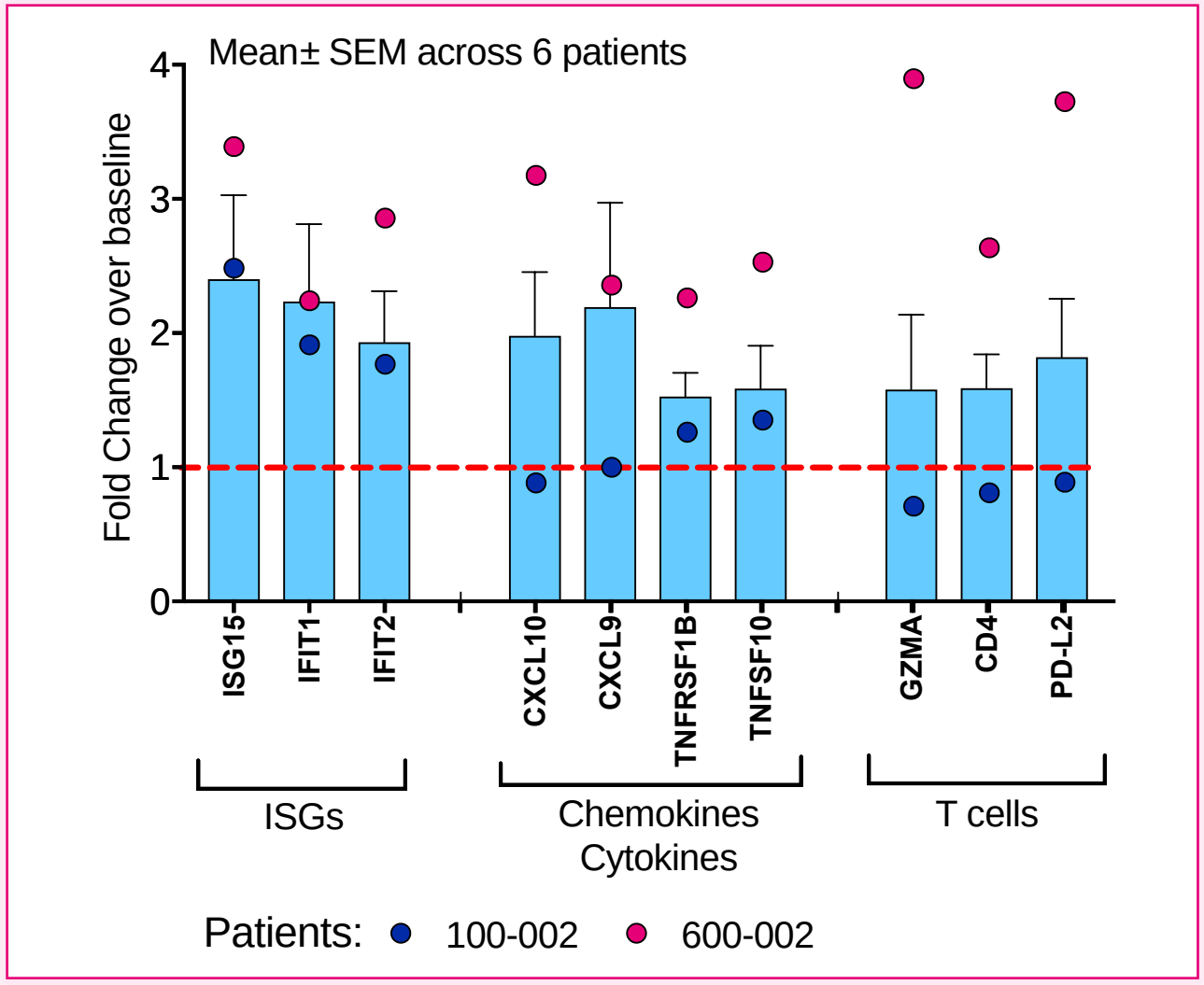
Th-1 T cell



As dose increases cytokine levels also increase

Tumor nanostring data suggest target engagement

6 Patients Dosed at 1e6 -1e7 Live Cells



Most upregulated genes across 6 patients in different categories
(fold change over baseline)

ISGs – Interferon-Stimulated Genes

CXCL9/10 – Chemokines inducing immune cell migration to tumor (Th1, CTLs, NK cells)

TNF/R superfamily – induce tumor apoptosis

Granzyme A (**GZMA**) – induce tumor cytotoxicity

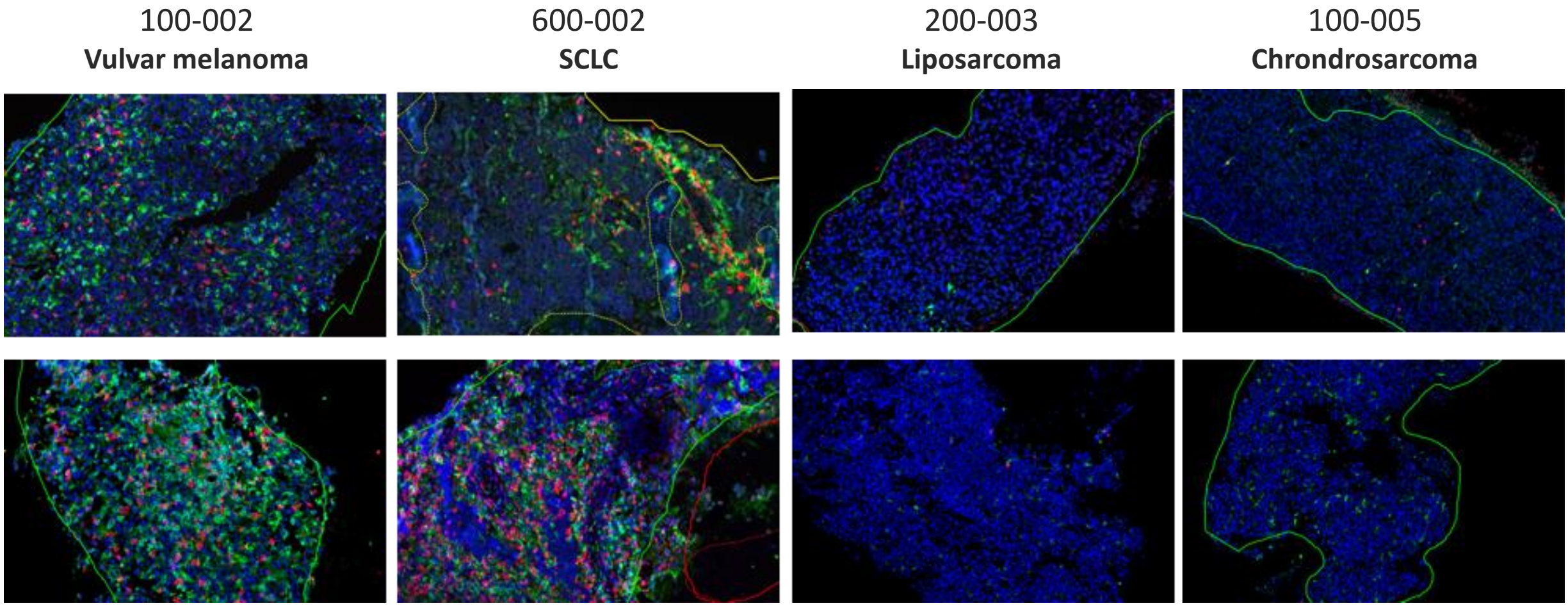
CD4 – CD4+ T cells

PD-L2 – Ligand for PD-1 (checkpoint receptor)

Biopsies pre-treatment – *Performed on injected lesion in week 4 (7 days after the third weekly dose)*

Multiplex immunofluorescence staining (IF) for tumor cores

Representative images from the patients: Enhanced T cell signal in "warm" tumors



DAPI (nucleus), CD4+ cells, CD8+ cells

Patient 100-002: Stable disease at 7 months with ensuing progressive disease

Metastatic Vulvar Melanoma previously treated with Nivolumab

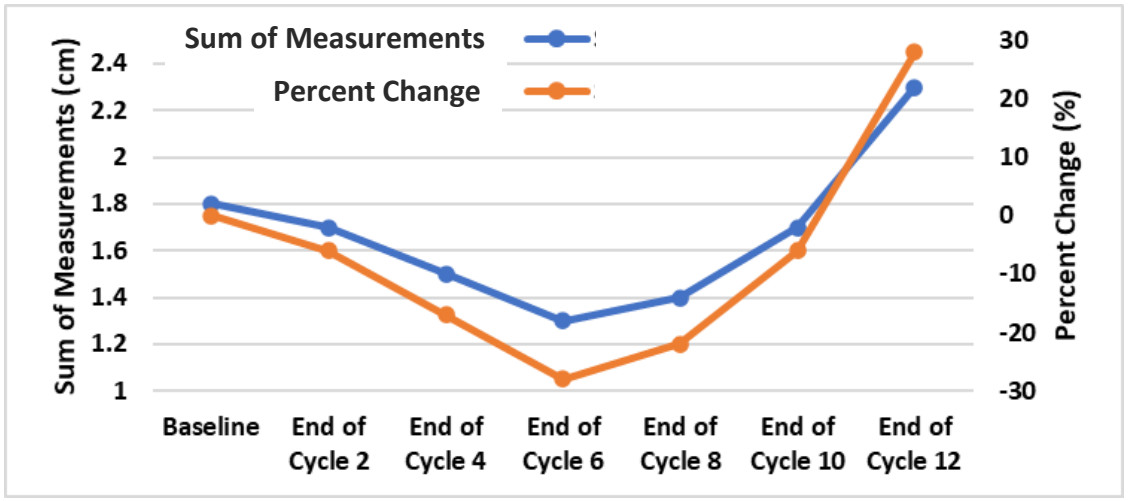
Stable disease, prior Nivolumab

63-yo Female dosed with 1e6 cells

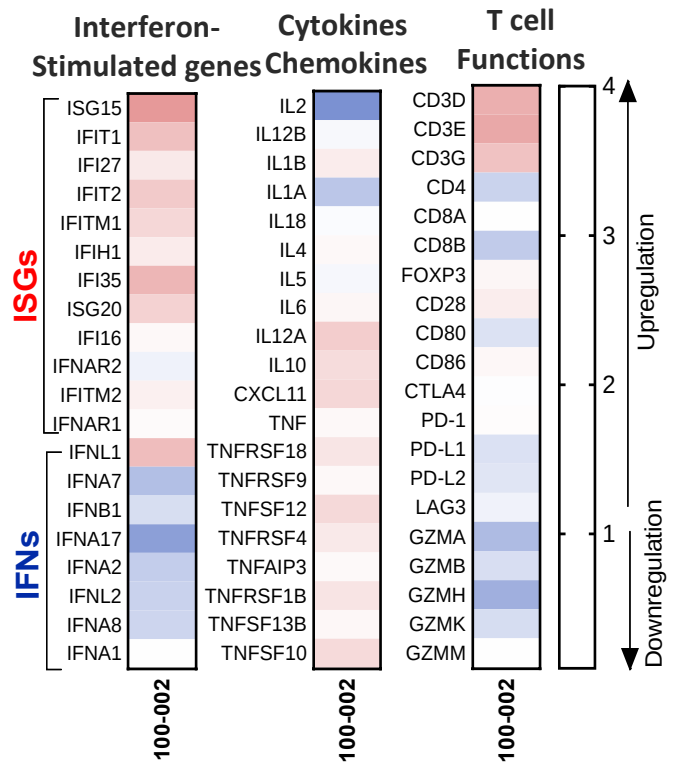
Previous Treatment: Local resection, nivolumab *(see note)*
Adverse Events: Itching, Hypoglycemia, Anxiety, Atrial fibrillation

Patient history: On nivolumab from 30 Jan 2019 to 06 Nov 2019 with PD
Subject started treatment (C1D1) with SYNB1891 on 10 Jul 2020.
KIT/PDGFRA/KDR Amplification. ATM Deletion

Tumor reduction (cm/%)



Strong upregulation of INF pathway & T cell response



NanoString data analysis (Baseline tumor vs Cycle 2 Day 1 tumor):

- Multiple ISGs ↑ - STING pathway engagement
- IL-10, IL-12A and CXCL-11 upregulation
- Small changes in tumor T cell compartment

Patient 600-002: imaging results indicate stable disease at >7 months

Small cell lung cancer previously treated with Pembrolizumab

Stable disease, prior Pembro

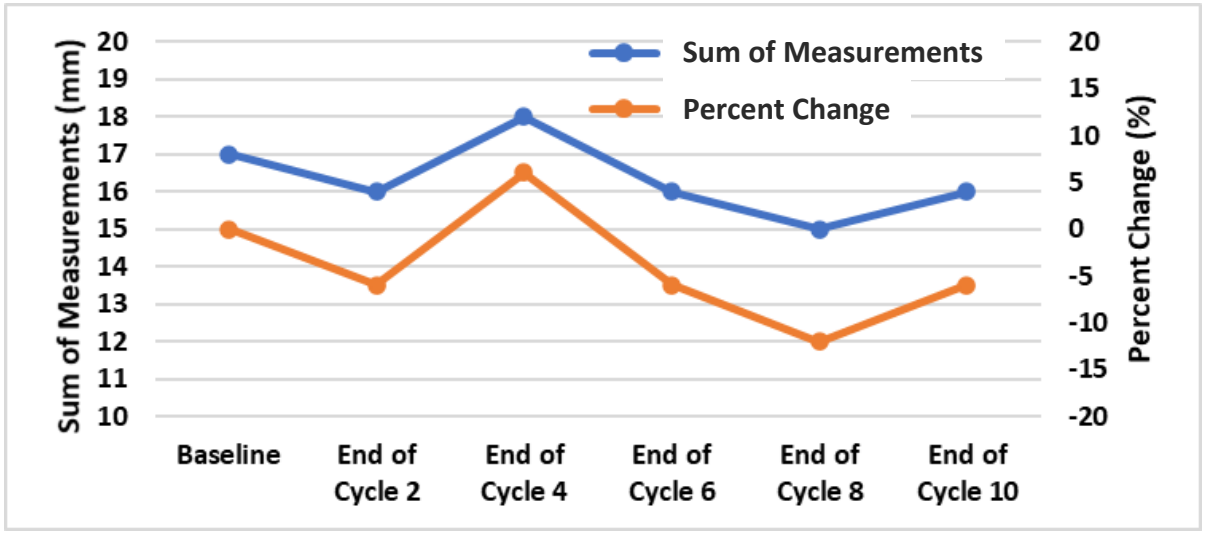
55-yo Female dosed with 1e7 cells

Previous Treatments: Etoposide/carboplatin, Pegzilarginase, Pembrolizumab

Adverse Events: Hyponatremia – mild, not related, Bradycardia – mild, related

Patient History: On pembrolizumab for 14 months: 13 Mar 2019 to 27 May 2020 with PD . Subject started treatment (C1D1) with SYNB1891 on 01 Jul 2020

Tumor reduction (cm/%)



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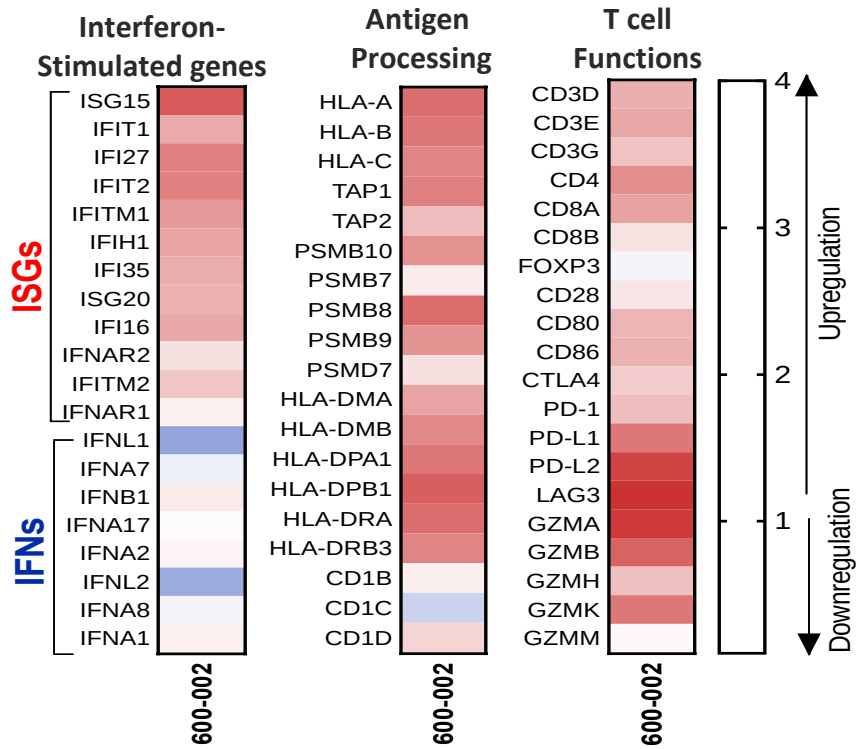

Cytokines: Modest ↑ in serum INFγ an IL-1Rα but not in IL-6 or TNF- α

NanoString

STING: Multiple ISGs upregulated

Chassis: ↑chemokines, cytokines and TLRs genes

T cell compartment: ↑↑ antigen processing and T cell function genes

SYNB1891 safe and well tolerated, data supports continued study

SYNB1891 is **safe and well-tolerated** as an intratumoral injection in a heterogenous population.

No dose limiting toxicities or infections

Dose levels through 1e7 live cells **demonstrate target engagement** as assessed by increases in serum cytokines, upregulation of ISGs and presence of tumor infiltrating lymphocytes

Evidence of **durable stable disease** was seen in 2 patients and was associated with upregulation genes tied to immune activation and increased intratumoral lymphocytes

These data support continued dose escalation in the monotherapy arm and combination arm with atezolizumab

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