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Systemic responses to SYNC-T therapy: *in situ* personalized cancer vaccination with intratumoral infusion of multi-target immunotherapy in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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April 7, 2024 | Session Title: Cancer Vaccines: Ready for Prime Time?

Disclosure Information

I have the following relevant financial relationships to disclose:

- Board Member: QSAM Biosciences, NovaScan, Syncromune
- Stockholder in: Syncromune, QSAM Biosciences, NovaScan, Perspective Therapeutics
- Employee of Syncromune

Immunotherapy Has Demonstrated Limited Responses in mCRPC

- Prostate cancer is considered an immunologically "cold" tumor with low expression of PD-L1, limited T cell infiltration, low tumor mutation burden, and an immunosuppressive TME
- These treatment barriers have proved to be challenging for systemic intravenously administered immunotherapies
  - Response rates to anti-PD-1 Abs are low (ORR 3-5%)[1] and checkpoint studies have shown little to no overall survival benefit [2-5]
  - Combination anti-PD-1 + anti-CTLA-4 has also demonstrated low response rates, with ORRs of 0-25%[6,7]
  - Significant rates of Grade 3 and 4 toxicity, especially with checkpoint combinations[6,7]
    - 42 – 53% Grade 3-4 treatment-related adverse events (TRAEs)
    - 26 – 40% discontinuation due to TRAEs
- **Currently the ability to combine targeted biologics is limited because of systemic autoimmune side effects**

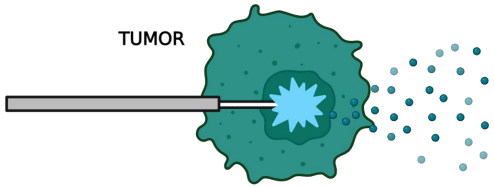
1. Antonarakis ES, et al. J Clin Oncol 38:395-405
2. Petrylak DP, et al., *JCO* 41, 19-19(2023).DOI:10.1200/JCO.2023.41.6_suppl.19
3. Kwon ED, et al. Lancet Oncol. 2014 Jun;15(7):700-12. doi: 10.1016/S1470-2045(14)70189-5.
4. Powles T., et al. Nat Med. 2022 January; 28(1):144-153. doi:10.1038/s41591-021-01600-6.
5. Graff JN, et al. Future Oncol. 2021 Aug;17(23):3017-3026. doi: 10.2217/fon-2020-1008.
6. Sharma P., et al. Cancer Cell. 2020 Oct 12;38(4):489-499.e3. doi: 10.1016/j.ccell.2020.08.007..
7. Shenderov E, et al. Prostate. 2021 May;81(6):326-338. doi: 10.1002/pros.24110.

SYNC-T Therapy Design

- Provide personalized *in situ* cancer vaccine for tumor antigen recognition
- Utilize multi-target approach to address multiple immune suppression mechanisms simultaneously
- Focus on reversing immune suppression in the TME and tumor draining lymph nodes to create systemic anti-tumor immunity
- Employ locoregional targeting that allows for lower dose administration, high local concentrations, less systemic exposure, and reduced toxicity

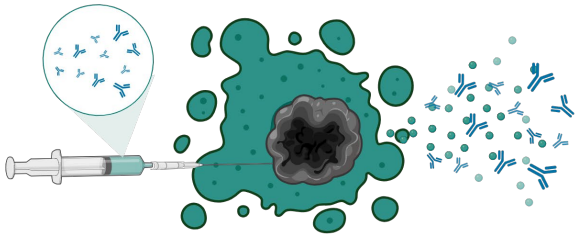
SYNC-T Personalized *In Situ* Therapy

A PORTION OF THE TUMOR IS LYSED USING TARGETED FREEZING



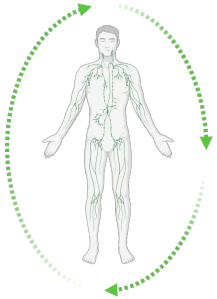
Tumor Antigens & DAMPs release

SV-102 BIOLOGIC INFUSED INTO LYTIC ZONE



Multi-targeted immune activation within the TME and regional lymph nodes leads to T cell activation and proliferation

SYSTEMIC ANTI-TUMOR RESPONSE



Tumor-specific T cells migrate and attack tumors systemically

Figure created using BioRender

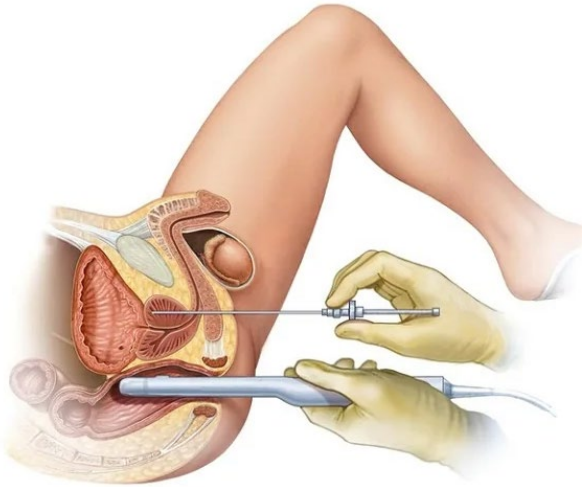
SYNC-T Therapy with SV-102 Proposed Mechanism of Action

- After oncolysis, tumor antigens are released from the target tumor lesion creating an *in situ* personalized vaccine
- **SV-102** fixed dose, multi-target biologic is comprised by the following APIs:
  - **609A – anti-PD-1 mAb**
    - Blocking PD1 allows T cells to effectively kill target cancer cells
  - **YH001 – anti-CTLA-4 mAb**
    - Enhances anti-tumor responses by blocking CTLA4 , allowing CD28 to bind CD80/CD86 to stimulate T cell priming, and also by downregulating Treg suppression
  - **YH003 - CD40 agonistic mAb**
    - Activates APCs
  - **HP007 - CpG-ODN (TLR9 agonist)**
    - Stimulates plasmacytoid dendritic cells and enhances Th1 mediated anti-tumor responses and stimulates APCs in the tumor draining lymph nodes
- The reversal of immune suppression results in effective antigen presentation, T cell activation, and proliferation

SYNC-T Therapy Procedure for mCRPC

The SYNC-T Therapy uses clinical procedural skills that are already routine for Urologists:

- Procedure employs commonly used MR and/or transrectal ultrasound (TRUS) imaging modalities for probe placement in the prostate
- First, oncolysis is performed via targeted freezing which is achieved using the ICESPHERE™ Cryoablation Needle to generate ~ 10 mm ice ball, followed by passive thawing
- After passive thawing, 15 ml of the SV-102 multi-target biologic is infused at a rate of 3 ml/min
- If distant soft tissue metastases (instead of prostate lesion) are the target for oncolysis, CT- guided needle placement is used



TRUS-Guided Transperineal Approach

SYNC-T with SV-102 Phase 1 Trial Inclusion & Exclusion Criteria

Investigator-initiated trial evaluating safety and efficacy of SYNC-T SV-102 Therapy for mCRPC

Open label, single arm study

KEY INCLUSION CRITERIA

- Metastatic histologically confirmed castrate-resistant prostate cancer
- Failure of previous treatment with one or more approved second-generation androgen-receptor-pathway inhibitors with or without prior chemotherapy or refused hormone therapy and chemotherapy
- Measurable disease by RECIST criteria
- Soft-tissue disease that can be targeted by SYNC-T Therapy
- Ability to provide informed consent

KEY EXCLUSION CRITERIA

- Known other primary malignancy other than prostate cancer that is progressing or has required active treatment in previous 3 years
- Obstructed urinary system before or after stenting
- Undergone major surgery or local prostate intervention within 28 days prior to first SYNC-T cycle
- Active infection requiring systemic therapy
- Received a live vaccine within 30 days prior to enrollment
- Significant cardiac or other medical illness

SYNC-T with SV-102 Phase 1 Trial Design & Endpoints

TRIAL DESIGN

- Up to 12 cycles of SYNC-T SV-102 at 4-week intervals to achieve best response
- Oncolysis combined with SV-102 fixed dose of 15 ml volume
- Baseline imaging of bone scan and/or PET/CT, and MRI of prostate
- Response assessment every 8 weeks
- Durability of response measured every 12 weeks after completion of therapy

ENDPOINTS

PRIMARY

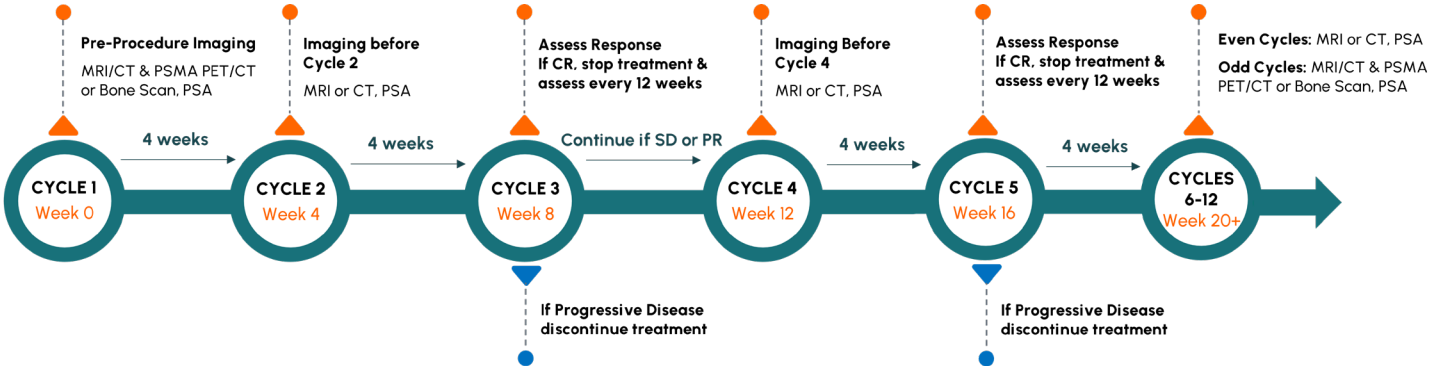
- Evaluate safety & toxicity

SECONDARY

- ORR by RECIST 1.1
- rPFS by PCWG3
- OS
- ORR by iRECIST

EXPLORATORY

- Assess pharmacokinetics and immunogenicity of each SV-102 API
- Exploratory biomarker analysis



Subject Demographics

- 15 subjects enrolled as of 10 January 2024
- Data is as of 9 March 2024

Race	White	60%
	Hispanic	33%
	Black	7%
Age	Median: 61 (Range: 49-74)	
ECOG	PS-0	40%
	PS-1	53.3%
	PS-2	6.7%

Prior Therapy

- 13 subjects evaluable as of 9 March 2024

Prior Therapy	ADT and/or 2nd generation anti-androgen or subject refused	100%
	Chemotherapy	23%
	Radiation Therapy	38%
	Immunotherapy	15%

SYNC-T SV-102 Response Summary

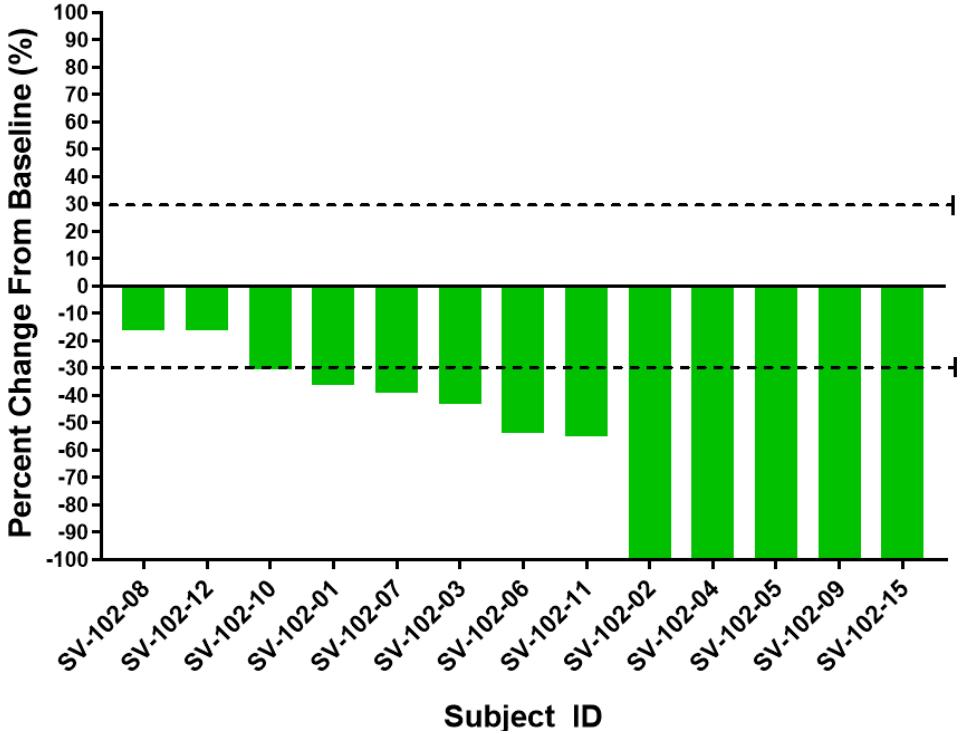
Subject	# Cycles	Best Response
SV-102-01	3	Partial Response
SV-102-02	2	Complete Response
SV-102-03	9	Partial Response
SV-102-04	5	Complete Response
SV-102-05	2	Complete Response
SV-102-06	6	Partial Response
SV-102-07	5	Partial Response
SV-102-08	2	Stable Disease
SV-102-09	7	Complete Response
SV-102-10	5	Partial Response
SV-102-11	5	Partial Response
SV-102-12	4	Stable Disease
SV-102-13	3	Not yet evaluable
SV-102-14	3	Not yet evaluable
SV-102-15	2	Complete Response

Best Response in Evaluable Subjects (n=13)	
Overall Response Rate	84.6%
Stable Disease	15.4%
Partial Response	46.1%
Complete Response	38.5%
Complete Resolution of Bone Metastases	53.8%
Progressive Disease	0%

- All CRs had a PSA < 2 when they achieved their response
- 2 subjects have died off study

NCT05544227 – Data presented as of 9 Mar 2024; all patients enrolled by 10 Jan 2024. Total N = 15 patients

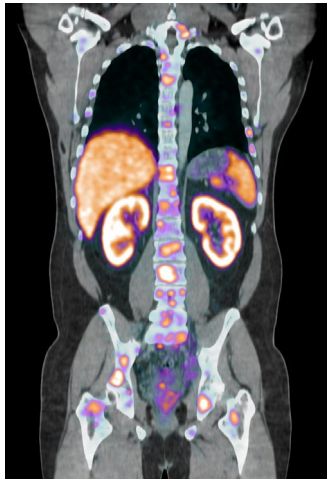
RECIST 1.1 Assessment



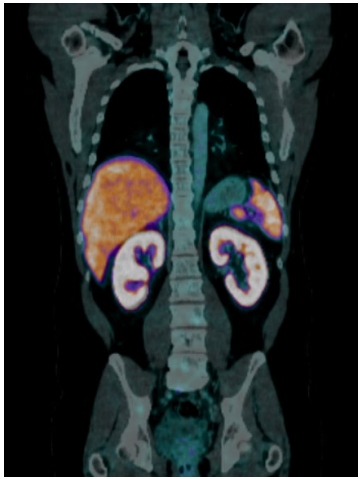
- 84.6% ORR (to date)
- 38.5% CR (to date)
- 46.1% PR (to date)
- 15.4% SD (to date)
- > 50% complete resolution of bone metastases (ongoing)

Subject SV-102-09: Complete Response

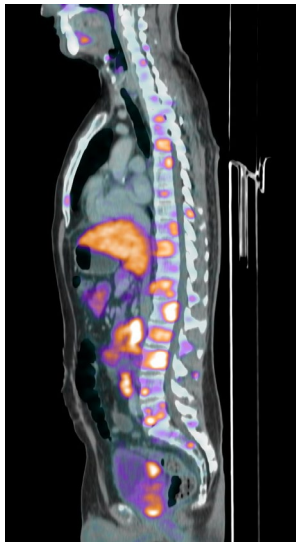
- Subject was confirmed via RECIST as a Complete Response
- Tumor was PD-1/ PD-L1 NEG and proficient MMR
- rPFS: 200+ days



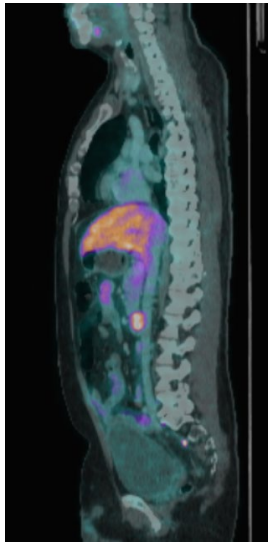
PRE-THERAPY. 5/2023 coronal PSMA PET/CT shows extensive bone metastases (greater than 50)



POST-THERAPY. 12/2023 coronal PSMA PET/CT shows complete resolution of all bone metastases



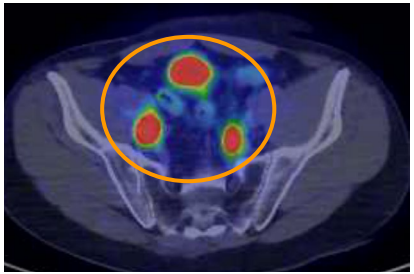
PRE-THERAPY. 5/2023 sagittal PSMA PET/CT shows extensive bone metastases



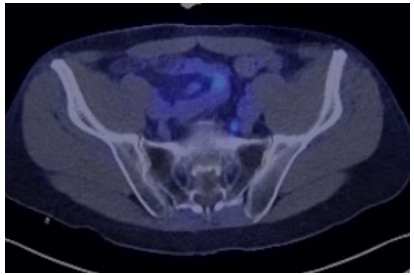
POST-THERAPY. 12/2023 sagittal PSMA PET/CT shows complete resolution of all bone metastases

Subject SV-102-04: Complete Response

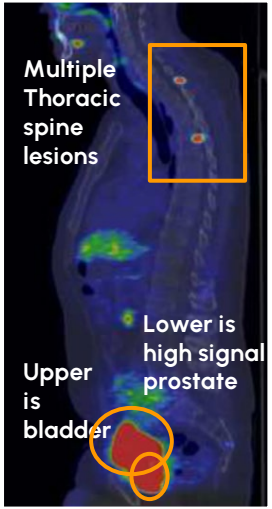
- After Cycle 4, subject was confirmed via RECIST and PCWG3 as a Complete Response with resolution of bone metastases, lymph node metastases and prostate
- rPFS: 261 days



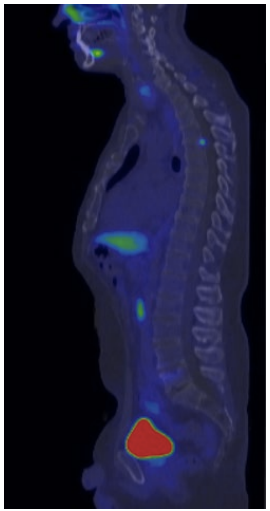
PRE-THERAPY. 3/2023 axial view shows a markedly abnormal PSMA PET/CT, high SUV in prostate, pelvic lymph nodes, and spine



POST-THERAPY. 9/2023 axial PSMA PET/CT showing minimal signal uptake in posterior aspect on T4



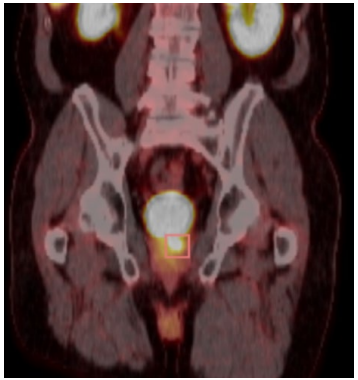
PRE-THERAPY. 3/2023 sagittal view shows a markedly abnormal PSMA PET/CT, high SUV in prostate, pelvic lymph nodes, and spine



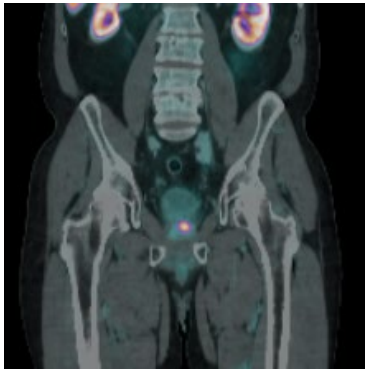
POST-THERAPY. 9/2023 sagittal PSMA PET/CT showing resolution of disease

Subject SV-102-03: Partial Response

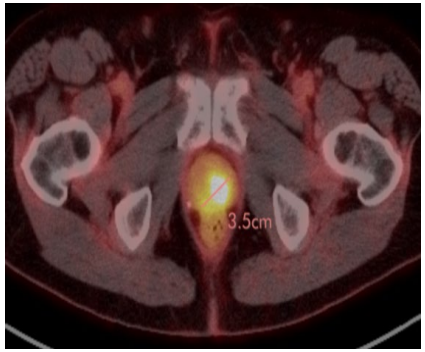
- Subject was confirmed via RECIST as a Partial Response after 1 cycle of SYNC-T
- Bone lesions are resolved in addition to near complete resolution in prostate.
- rPFS: 332+ days



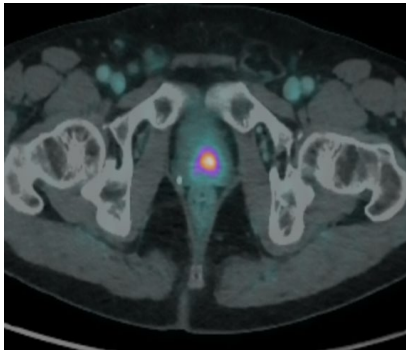
PRE-THERAPY. 2/2023: PSMA PET/CT coronal scan at baseline shows extensive involvement in prostate and in left 10th rib



POST-THERAPY. Follow-up PSMA PET/CT from 10/2023 coronal image showing resolution of bone lesion and significant reduction in prostatic disease



PRE-THERAPY. 2/2023: PSMA PET/CT axial scan at baseline shows prominent 3.5 cm lesion in both lobes of the prostate, appearing to involve the capsule



POST-THERAPY. Follow-up PSMA PET/CT from 10/2023 coronal image showing resolution of bone lesion and significant reduction in prostatic disease

Safety and Tolerability

	All TEAEs		Grade 1+2 TEAEs		Grade >=3 TEAEs	
Term	(N=15) n (%)	Events	(N=15) n (%)	Events	(N=15) n (%)	Events
Any Treatment Emergent Adverse Events (TEAEs)	13 (86.7)	31	12 (80.0)	29	2 (13.3)	2
Fever	3 (20.0)	4	3 (20.0)	4	0	0
Hematuria	3 (20.0)	3	3 (20.0)	3	0	0
Diaphoresis	2 (13.3)	2	2 (13.3)	2	0	0
Urinary Retention	2 (13.3)	2	1 (6.7)	1	1 (6.7)	1
Vomiting	2 (13.3)	2	2 (13.3)	2	0	0
Diarrhea	1 (6.7)	1	1 (6.7)	1	0	0
Acute Urinary Retention	1 (6.7)	2	1 (6.7)	2	0	0
Anemia	1 (6.7)	1	1 (6.7)	1	0	0
Chest Pain	1 (6.7)	1	1 (6.7)	1	0	0
Diarrhea	1 (6.7)	1	1 (6.7)	1	0	0
Fatigue	1 (6.7)	1	1 (6.7)	1	0	0
Hepatic Enzymes Increased	1 (6.7)	1	1 (6.7)	1	0	0
Myalgias	1 (6.7)	2	1 (6.7)	2	0	0
Polydipsia	1 (6.7)	1	1 (6.7)	1	0	0
Rash Cutaneous	1 (6.7)	1	1 (6.7)	1	0	0
Rectal Discomfort	1 (6.7)	1	1 (6.7)	1	0	0
Right Shoulder Fracture	1 (6.7)	1	1 (6.7)	1	0	0
Skin Squamous Cell Carcinoma	1 (6.7)	1	1 (6.7)	1	0	0
Spinal Cord Compression	1 (6.7)	1	0	0	1 (6.7)	1
Urethral Discomfort	1 (6.7)	1	1 (6.7)	1	0	0
Urinary Tract Infection	1 (6.7)	1	1 (6.7)	1	0	0

Dose & Exposure of SV-102 With Individual Components

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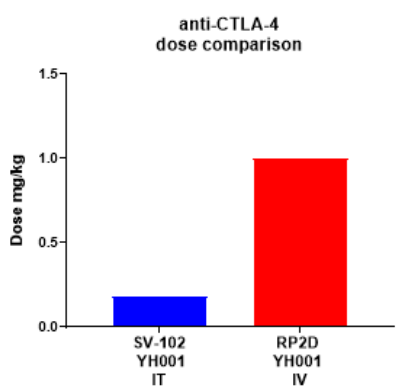
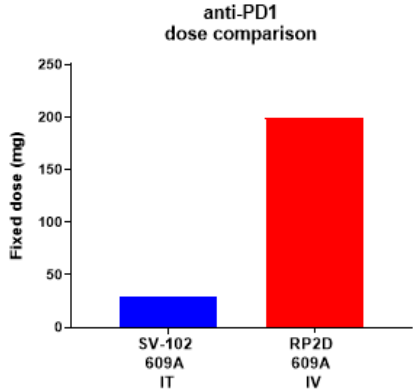
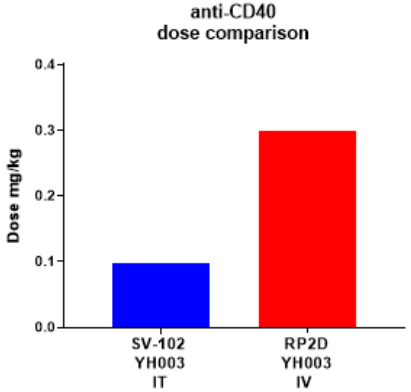
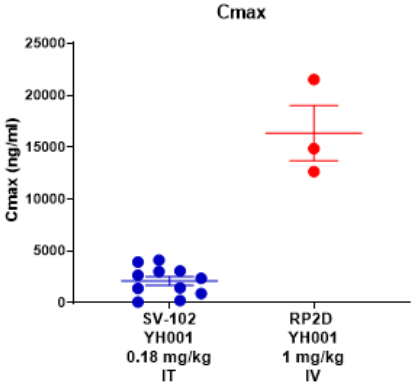
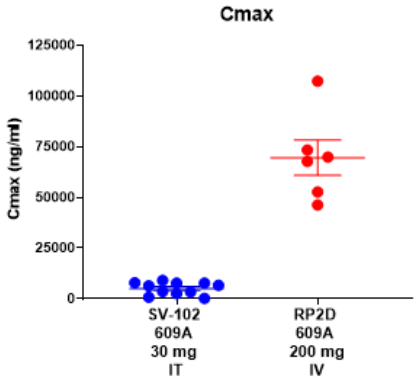
- APIs in SV-102 are dosed at much lower levels than IV RP2D
- Much lower systemic exposure is observed

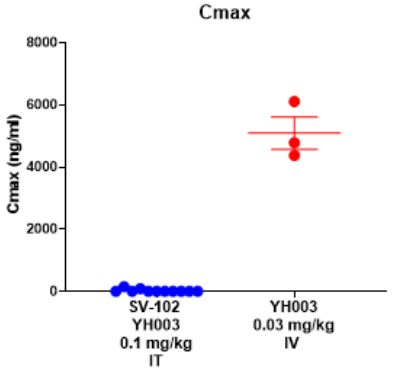




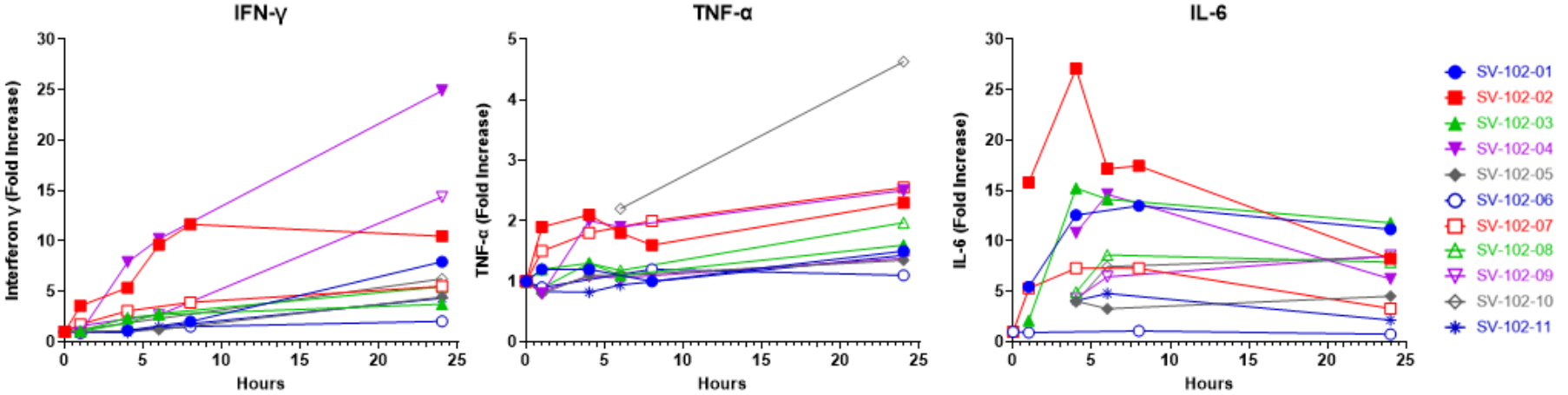








Anti-Tumor Cytokines Are Rapidly Induced by SYNC-T Therapy*



- Pro-inflammatory cytokines increase during the first 24 hrs after SYNC-T Therapy
- IFNγ, TNFα and IL-6 all show significant increases from pre-treatment

* Data from first 11 subjects

Conclusions

- SYNC-T Therapy with SV-102 for mCRPC demonstrates highly encouraging clinical activity.
- Significant portion of patients in this pilot study have achieved either a complete response or near complete response with resolution of all bone metastases.
- Initial safety data demonstrated no grade 3 or 4 autoimmune adverse events in this pilot study.
- Overall systemic drug expose after SYNC-T Therapy intratumoral infusion is significantly lower than IV infusion.
- Further study of SYNC-T Therapy is warranted and ongoing.

Acknowledgements

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