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Phase I study of intratumoral administration of CF33-hNIS-antiPD-L1 (CHECKvacc) in patients with metastatic triple negative breast cancer

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BACKGROUND

- CF33-hNIS-anti-PD-L1 (CHECKvacc) is a novel chimeric orthopoxvirus with robust anti-cancer activity in TNBC xenografts.
- Human sodium-iodide symporter (hNIS) gene transfer allows tracking of virus by 99mTc single-photon emission computed tomography (SPECT).
- Our preliminary animal studies demonstrated that tumor cells infected with CHECKvacc successfully secrete functional hNIS and single-chain variable fragment (scFv) against programmed death ligand-1 (PD-L1).
- In pre-clinical studies, CHECKvacc administered by intratumoral injection appears safe and is well-tolerated.
- CHECKvacc detects and effectively kills TNBC at doses several magnitudes lower than other oncolytic viruses (OVs) in xenograft models.

METHODS

- This study is a first-in-human phase I, single center, single arm clinical trial evaluating the safety and tolerability of CHECKvacc intratumoral injection in patients with mTNBC.
- The first 3 subjects of dose level 1 were enrolled sequentially for safety monitoring.
- Once the initial 3 subjects were treated sequentially, the study followed the Phase I Queue 3+3 (IQ 3+3) design which expands a dose level up to 8 subjects after a single DLT has been observed.
- Enrollment to the final RP2D may be expanded to include up to 12 patients for efficacy assessment. The estimated targeted accrual is 33 patients (minimum) to 78 patients (maximum).
- Correlative aims include assessing viral kinetics, viral plaque assay, 99mTc SPECT imaging for virus tracking, peripheral blood and tumor tissue for antiviral immune activation, and tumor microenvironment changes in association with response to therapy.

OBJECTIVES

•Primary objective is to evaluate the safety and tolerability of CHECKvacc by CTCAE v5.0.

•Secondary objectives are to determine recommended phase II dose (RP2D) and response rate by RECIST1.1 and irRECIST.

•Exploratory objectives are to determine optimal biologic dose (OBD); antiviral immune activation as determined by increased expression of PD-1, PD-L1, or CTLA-4 and increased CD8+ cells; viral kinetics, and viral infection using hNIS-based imaging such as technetium scan and viral plaque assays.

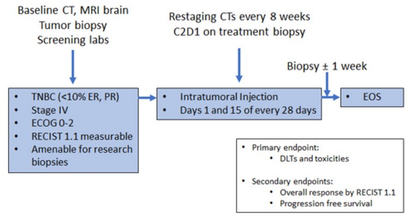

Figure 1. Study schema. Primary endpoints are DLT and toxicities by CTCAE v5.0.; Secondary endpoints are OS by RECIST 1.1 and irRECIST 1.1 and PFS. CT, computerized tomography; MRI, magnetic resonance imaging; C2D1, cycle 2 day 1; TNBC, triple negative breast cancer; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; EOS, end of study; DLT, dose limiting toxicity; CTCAE, common terminology criteria for adverse events

ELIGIBILITY CRITERIA

•Histologically confirmed metastatic triple negative breast cancer (TNBC) defined as ER and PR ≤ 10% by IHC, and HER2 negative per ASCO/CAP guidelines

•Measurable disease by RECIST 1.1, ECOG ≤ 2

•Patients must have progressed or been intolerant of at least 2 prior lines of systemic chemotherapy for advanced/metastatic disease

•Must have a superficial tumor (cutaneous, subcutaneous), breast lesion or nodal metastases amenable to safe repeated intratumoral injections per treating physician and interventional radiologist review.

EXCLUSION CRITERIA

•Chemotherapy within 14 days

•Surgery or radiation within 28 days

•Uncontrolled brain metastasis

•Vaccination within 30 days, active infections

•Pregnant or breast feeding.

Table 1. Dose levels

Cohort	Dose (PFU)*	Number of doses
-1	3×10^4	6
+1	1×10^5	6
+2	3×10^5	6
+3	1×10^6	6
+4	3×10^6	6
+5	1×10^7	6
+6	3×10^7	6
+7	1×10^8	6

*Dose -1 is needed only if dose level 1 is not tolerated.

Table 2. All AEs regardless of attributions (N=6)

DOSE LEVEL	AE	Grade 1	Grade 2	Grade 3
DL1: 1 x 10^5 (n=3)	Pain in extremity		1	
	Creatinine increased		1	
	Hyperglycemia	1		
	Nausea	1		
	Vomiting	1		
	Pain	1		
	Neck stiffness	1		
DL2: 3 x 10^5 (n=3)	Fatigue	1		
	Hyponatremia	1		
	Nasal congestion	1		
	Sore throat	1		
	Chest wall discomfort	1		
	Injection site discoloration	1		

STATISTICAL DESIGN

- The first 3 subjects will be enrolled sequentially, with each receiving a single injection and completing the 4-week safety evaluation before the next is treated. Subsequent enrollment and dose escalation will be according to the Phase I Queue (IQ) 3+3 design.
- At most 3 subjects will be in the 4-week first evaluation period (day 1 injection, day 15 injection, day 29 evaluation) at any time. At least 3 subjects must complete the first evaluation period (or have DLT) before a dose escalation decision can be made.
- Prior to the determination of the RP2D, patients not evaluable for DLT considerations will be replaced within the same dose cohort. All treated subjects will be accounted for in reporting on safety, and all eligible patients who start treatment will be considered in the calculation of the response rate.
- -DLT is defined as any Grade 3 or 4 toxicities that are possibly related to CF33-hNIS-antiPDL1 (excluding some Grade 3 injection site reactions, rashes, fatigue, GI symptoms, and transient lab abnormalities)

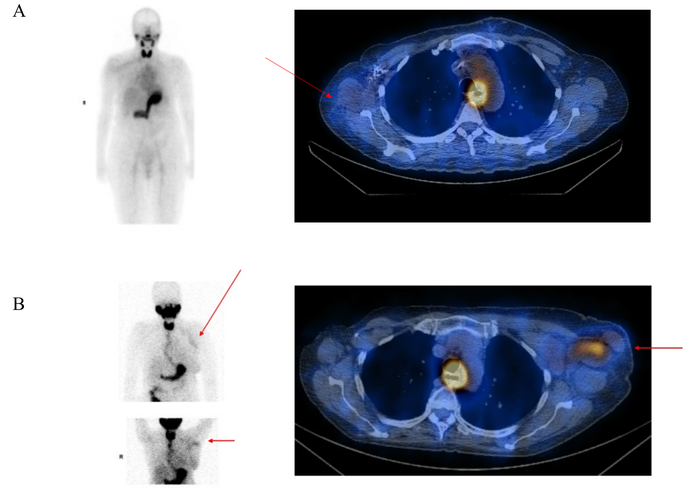

Figure 2. Comparison of SPECT imaging of two patients using Technetium-99m (C1D8). A) Patient COH-001 received CHECKvacc at DL1 ($1x10^5$ PFU). Injected lesion was right shoulder mass (baseline 38 x 34 mm; EOT 32 x 24 mm, SD); B) Patient COH-004 received CHECKvacc at DL2 ($3x10^5$ PFU). Injected lesion was left axilla (baseline 26 x 17 mm, EOT 32 x 21 mm, PD) showed significant enhancement of injected lymph node.

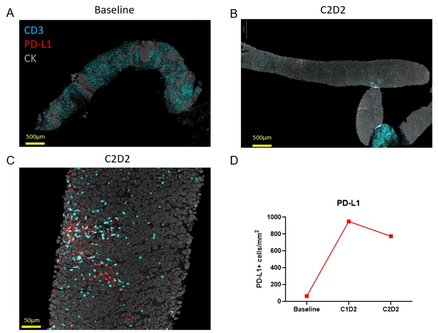

Figure 3. Multiplex immunofluorescence (mIF) of COH-004 tumor immune infiltrates. A) Baseline biopsy; B) C2D2 biopsy; C) Higher magnification of C2D2 biopsy; D) density of PD-L1+ cells across patient tissue biopsies. Scale bars as shown.

RESULTS

- From October 2021 to June 2022, 6 patients were enrolled in this ongoing study and received at least 1 dose of CHECKvacc injection at dose level 1 (1 x 10^5 pfu) or dose level 2 (3 x 10^5 pfu).
- The intratumoral CHECKVacc injections were well tolerated, and no DLTs were observed. No treatment related AEs were reported for 6 patients except 1 patient with injection site discoloration.
- 99mTc SPECT imaging for virus tracking shows enhancement in 4/6 (67%) patients in the first 2 dose levels. Enhancement was greater in patients with injection of nodal disease compared to dermal metastasis.
- SPECT imaging of patient COH-004 (DL-2) on C1D8 showed significant enhancement of injected lymph node.
- Responses: 1 SD and 5 PD.
- -Baseline and on-treatment tumor biopsies of patient COH-004 using spatial immune profiling showed an increase in PD-L1 positive cells following treatment with CHECKVacc.

CONCLUSION

CF33hNIS-antiPD-L1 administered by intratumoral injection in patients with mTNBC is safe and well tolerated at the dose levels tested.

ACKNOWLEDGEMENTS

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