Phase Ib Study of Pembrolizumab in Combination with Intratumoral Injection of Clostridium novyi-NT in Patients with Advanced Solid Tumors

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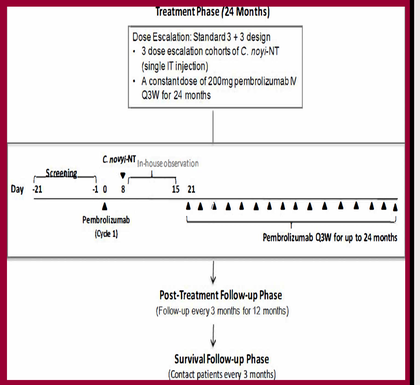
INTRODUCTION

Intra-tumoral (IT) Clostridium novyi-NT (non-toxic) is an attenuated strain of C. novyi lacking alpha toxin replication within hypoxic tumor regions, causing tumor cell lysis and inflammation.[1,2] Intravenous (IV) and IT treatment of naturally occurring solid tumors in canine with C. novyi-NT had previously demonstrated up regulation of the immune system.[3] This phase 1b dose escalation study assessed safety and potential synergistic effects of pembrolizumab and C. novyi-NT in advanced solid tumors.

METHODS

We enrolled patients with percutaneous injectable, solid tumors to receive single intratumoral injection of C. novyi-NT administered on Day 8 across 4 dose cohorts (3x10^4 to 100 x10^4 spores, 3+3 design) with pembrolizumab 200mg IV Q3weekly starting on Day 0 up to 24 months. Primary objectives: Safety, tolerability and maximum tolerated dose (MTD) of combination. Secondary objectives: anti-tumor activity of combination in the injected tumor lesion and overall response by iRECIST 1.1.

STUDY DESIGN



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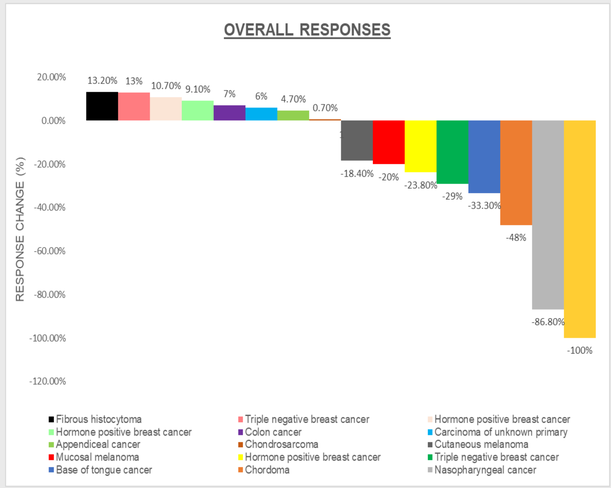
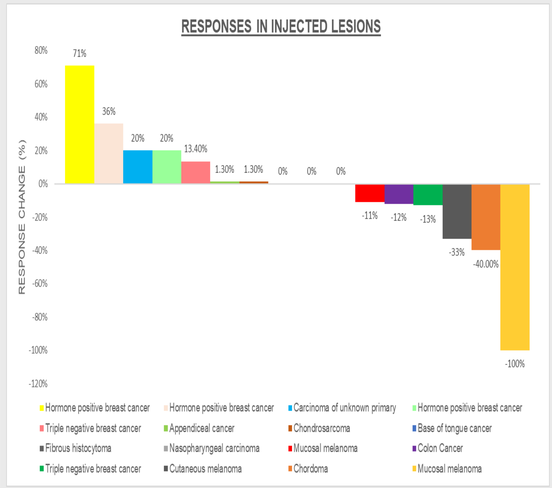
DEMOGRAPHICS

All Patients (n=16)		
Age (Median Range)		62.5 (40-71)
Sex	**Male**	5
n (%)	**Female**	11
ECOG	**0**	0
n (%)	**1**	16
	2	0
Ethnicity		
	African-American	3
	Asian	1
	Caucasian	12
	Hispanic	1
Median injected tumor size (range), cm		2.65 (1-11)
Prior Immunotherapy		8
Primary tumor, n (%)		
	Appendiceal Cancer	1 (6.25%)
	Breast Cancer (Invasive Ductal Type)	5 (31.25%)
	Carcinoma of Unknown Primary	1 (6.25%)
	Chordoma	1 (6.25%)
	Colon Cancer	1 (6.25%)
	Head and Neck Cancer	1 (6.25%)
Melanoma	**Cutaneous**	1 (6.25%)
Melanoma	**Mucosal**	2 (16.5%)
	Nasopharyngeal Cancer	1 (6.25%)
Sarcoma	**Fibrous Histiocytoma**	1 (6.25%)
	Myxoid Chondrosarcoma	1 (6.25%)
Prior lines of systemic therapies, n (%)		3 (1-10)
	0–1	1
	2–3	8
	4–5	2
	> 5	5
Patient Status	**Alive**	7
Patient Status	**Dead**	8
Patient Status	**Unknown**	1
Patient Status	**On Trial**	3
Median number of cycles, (n)		5 (1-34)

EFFICACY





SAFETY

	All patients (n=16)		
	G1	G2	G3/4
Fever	3 (19%)	1 (6%)	0
Injection site reaction	4 (25%)	0	0
Abscess of Injected lesion	0	1 (6%)	0
Necrosis of Injected Site	1 (6%)	1 (6%)	0
Skin Rash	1 (6%)	1 (6%)	0
Diarrhea	1 (6%)	0	0
Leukocytosis	1 (6%)	0	0
Pruritus	2 (13%)	0	0
Leukopenia	2 (13%)	1 (6%)	0
Neutropenia	1 (6%)	0	0
Anemia	2 (13%)	0	0
Lymphopenia	1 (6%)	0	0
Hyperglycemia	1 (6%)	0	0
Fatigue	1 (6%)	0	0
Lymphedema	1 (6%)	0	0

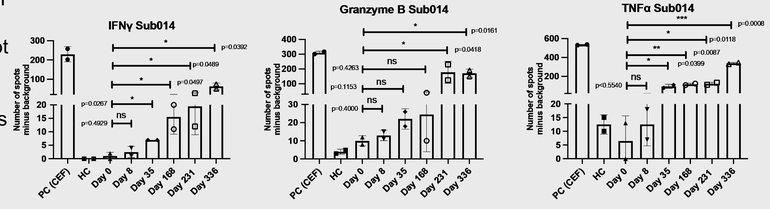
CONFIRMED RESPONSES

	Injected Lesion Response	Overall Response
CR	1 (6%)	1 (6%)
PR	2 (13%)	3 (19%)
ORR	3 (19%)	4 (25%)
CBR: CR+PR+SD >6 MONTHS	3 (19%)	4 (25%)
PD	4 (25%)	1 (6%)
SD	9 (56%)	11 (69%)

TRANSLATIONAL FINDINGS

T-cell cytokine responses in PBMCs of a patient with nasopharyngeal cancer and best overall response of PR (-86.8%) per RECIST criteria

Tumor antigen stimulated release of T-cell IFNγ, TNFα, and granzyme B, were simultaneously measured by Immunospot following the pulse treatment of patient PBMCs with tumor cell extract. and was adjusted for background. Background was calculated based on response to patient PBMC to PBMC extract from healthy individuals.



DISCUSSION

- At data cutoff on October 24, 2022, 16 patients were enrolled.
- 10 patients (63%) experienced progression; 1 withdrew consent; 1 completed therapy; 1 came off trial due to toxicity (immune related dermatitis) and 3 patients remain on trial
- 8 (50%) received prior IO and 7 (44%) had > 4 lines of prior therapies.
- Confirmed overall objective response rate (ORR) was 25% in 4 patients [non-keratinizing undifferentiated nasopharyngeal squamous carcinoma, human papilloma virus positive squamous cell carcinoma of base of tongue, vulvar melanoma and chordoma] with 3 partial responses and 1 complete response.
- Most prevalent grade 1 and 2 adverse events were injection site reaction (25%), pyrexia (19%), pruritus (13%), leukopenia (13%) and anemia (13%). No grade 3 or 4 treatment related adverse events noted.
- Signs and symptoms of C. novyi-NT germination including fever, injection site pain, erythema, swelling, tenderness, and in some cases, ulceration, spontaneous drainage, tissue sloughing, bleeding, and malodor were observed in 5 patients.

CONCLUSIONS

Intratumoral C. novyi-NT with pembrolizumab demonstrates clinical activity with favorable tolerability in patients regardless of tumor histology. This study is ongoing to define the recommended phase 2 dose (NCT03435952)

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