Abstract #

NANT Triple Negative Breast Cancer (TNBC) Vaccine: Molecularly-Informed Integrated Immunotherapy Combining Innate High-Affinity Natural Killer (haNK) Cell Therapy with Adenoviral & Yeast-based Vaccines and Immune Checkpoint Inhibitor to Induce T-Cell Responses in Subjects with TNBC Who Have Progressed on or after Standard-of-Care Therapy

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BACKGROUND

TNBC is an aggressive subtype of breast cancer with limited treatment options for which immunotherapy has demonstrated clinical benefit in selected patients [1]. We hypothesized rationally-based, thoughtfully-sequenced orchestration of both innate and adaptive immune system responses would elicit anti-tumor efficacy. We further hypothesize that by activating the entire immune system, the immunogenic cell death In this disease will be durable and associated with a low risk of adverse events. Here we describe a first-in-human novel combination immunotherapy protocol of chemoradiation, checkpoint inhibition, cytokine-induced NK & T cell activation [2], & off-the-shelf high-affinity NK (haNK) cell infusion.

METHODS

TNBC patients (pts) were enrolled in QUILT 3.067 (NCT03387085) that had either progressed on or after (or refused) anthracycline-based chemotherapy (or other SoC) or other taxane- and platinum-based therapies; had an ECOG performance status of 0 to 2; & had at least 1 lesion of ≥ 1.0 cm. Subject tumor tissue was to be biopsied for molecular analysis, and blood samples collected for isolation of peripheral blood mononuclear cells (PBMCs).

Figure 1: Rationale for Selection of Agents Included in NANT TNBC Protocol

Agent	Mitigating Immunosuppression in the TME	Inducing and Coordinating ICD Signals	Conditioning Dendritic and T Cells	Enhancing Innate Immune Responses	Maintaining Immune Responses
Aldoxorubicin HCl	X	X			
Avelumab					X
Bevacizumab	X	X			
Cisplatin		X			
Cyclophosphamide	X	X			
AdV (CEA, MUC1, Brachyury)			X		
5-FU or Capecitabine	X	X			
Yeast (Ras, CEA, Brachyury)			X		
haNK cells				X	
N-803			X	X	X
Nab-paclitaxel	X	X			
SBRT		X		X	

RESULTS

Figure 2. ***Demographics, Adverse events (AEs) & toxicity***. Nine TNBC pts have been treated to date in an outpatient setting. Eight of these had primarily chemotherapy-related neutropenia and/or anemia. Grade ≥3 haNK-related AEs (fever and fatigue) were observed in 3 pts. No patient withdrew due to SAEs. No pts experienced cytokine release syndrome.

DEMOGRAPHICS	N (%)
Age	49 (36-57)
Race: Caucasian	6 (67)
Hispanic	2 (22)
Asian	1 (11)
ECOG: 0,1	7 (78), 2(22)
Site of metastasis:	
Bone	4 (44)
Liver	3 (33)
Lung	6 (67)
Lymph node	8 (89)
Skin	1 (11)

GRADE 3 ADVERSE EVENT	N (%)
Subjects with at least 1 grade 3 or higher AE	9 (100)
Anemia	5 (56)
Neutropenia	6 (67)
Thrombocytopenia	1 (11)
Febrile neutropenia	1 (11)
Nausea	1 (11)
Fatigue	2 (22)
Pyrexia	5 (56)
Cholecystitis	1 (11)
Infection	3 (33)
Hyponatremia	1 (11)
Lymphedema	1 (11)

Figure 3. Response to treatment & progression-free survival (PFS). (A) The maximum target lesion response percent based on RECIST1.1 criteria is shown for each patient. To date, the (early) disease control rate (DCR) combining Complete Response, Partial Response, and Stable Disease (CR+PR+SD) is 78% (7/9 pts) and the Overall Response Rate (ORR - PR+CR) is 67% (6/9 pts) using irRC. Two pts (22%; 2/9) achieved a CR. (B) Median PFS is 13.7 months; seven (7) pts are alive, and the duration of responses ranges from 2 months to over 12 months. Four patients remain on study to date.

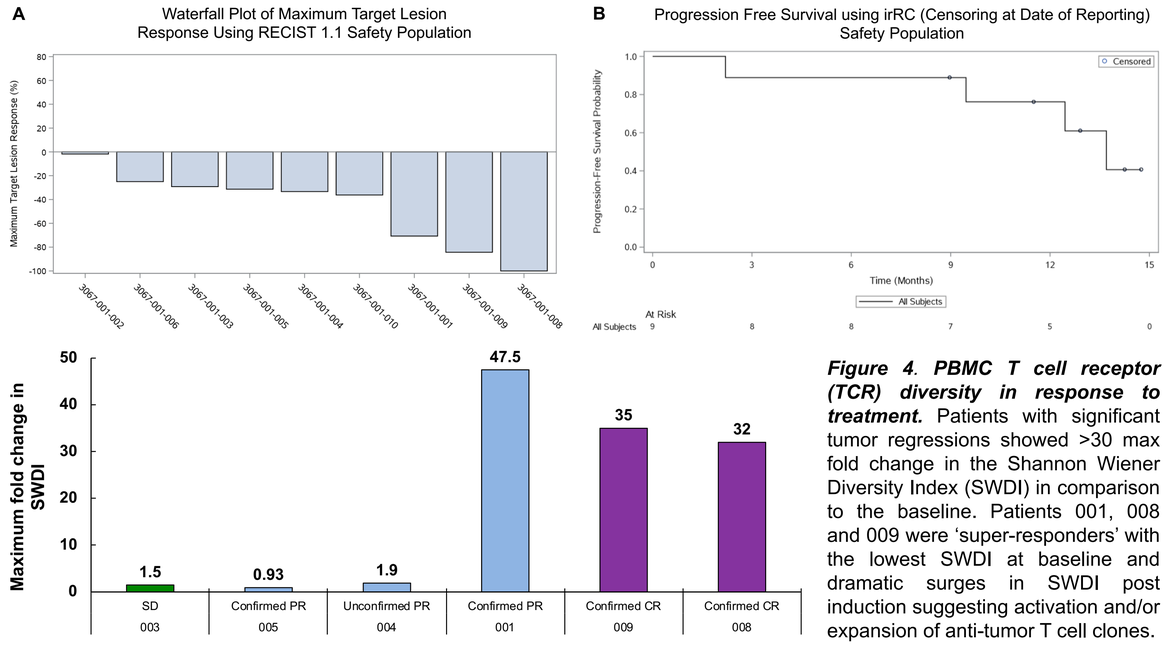

Figure 4. PBMC T cell receptor (TCR) diversity in response to treatment. Patients with significant tumor regressions showed >30 max fold change in the Shannon Wiener Diversity Index (SWDI) in comparison to the baseline. Patients 001, 008 and 009 were 'super-responders' with the lowest SWDI at baseline and dramatic surges in SWDI post induction suggesting activation and/or expansion of anti-tumor T cell clones.

KEY FINDINGS

- The Overall Response Rate (ORR) to orchestrated treatment in QUILT 3.067 is 67%
- Disease Control Rate (DCR) of 78%
- Complete Response (CR) rate of 22%.
- No cytokine release syndrome
- No patients withdrew due to SAEs
- Protocol was successfully administered exclusively in an outpatient setting.
- T cell receptor diversity shows potential as a predictive biomarker for response to the therapeutic approach used here.
- This novel combinatorial mechanism shows early efficacy.

CONCLUSIONS

The early efficacy of the novel, combinatorial, sequenced & orchestrated treatment approach presented here warrants further study in expanded clinical trials. In addition, the utility of TCR profile as a biomarker for response should be further explored & validated.

CONTACT

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REFERENCES

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