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Phase 1 dose escalation of ONT-10, a therapeutic MUC1 vaccine, in patients with advanced cancer

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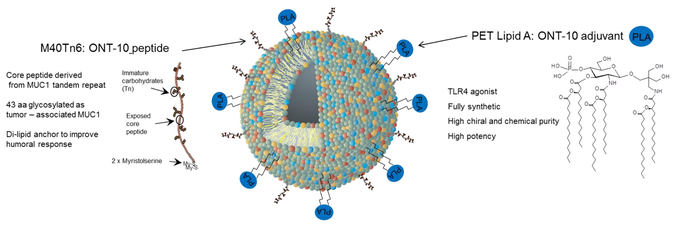
Background

MUC1 Antigen

- Mucin 1 (MUC1) is a transmembrane glycoprotein that is expressed at low levels on the apical surface of most glandular epithelial cells. Normal functions of MUC1 include contributing to barrier protection against pathogens and intracellular signaling via phosphorylation of the cytoplasmic tail.
- MUC1 is overexpressed, hypoglycosylated, and aberrantly localized in a large proportion of human malignancies. Its varied tumor-promoting mechanisms include enhancement of cell motility and metastasis, support of growth factor intracellular signaling, and inhibition of apoptosis.
- Overexpression of abnormal MUC1 is associated with poor prognosis in many cancers and the extracellular domain of MUC1 shed into the bloodstream (soluble MUC1) is known to be immunosuppressive. Two important diagnostic and prognostic cancer tests, CA15-3 and CA27-29, measure soluble MUC1.
- Importantly, antibody response to abnormal MUC1 has been associated with improved prognosis in multiple malignancies, including breast, gastric, lung, ovarian, and pancreatic cancers.

ONT-10 is a novel glycolipopeptide-based MUC1 liposomal cancer vaccine



- ONT-10 is a liposomal vaccine composed of a synthetic 43 amino acid (aa) glycolipopeptide (M40Tn6) incorporating two repeats of the MUC1 VNTR region and the potent synthetic TLR4 agonist PET Lipid A in a 2:1 ratio.
- The ONT-10 antigen is hypoglycosylated to mimic the abnormal glycosylation state of tumor-associated MUC1 and is designed to elicit both humoral and cellular immune response.
- PET Lipid A is a fully synthetic TLR4 agonist that in preclinical studies is approximately 10-fold more potent than MPL®, the TLR4 agonist used in commercial vaccines.
- In preclinical studies ONT-10 demonstrated potent and sustained activation of both humoral and cellular immunity to hypoglycosylated MUC1 and demonstrated anti-tumor activity in syngeneic mouse tumor models (L. Pestano et al., AACR 2011).

ONT-10 Phase 1 Study Objectives and Design

Objectives

- Primary: Safety, maximum tolerated dose/recommended dose
- Secondary: Immunogenicity of escalating doses of ONT-10
- Exploratory: MUC1 expression in archived tumor samples by immunohistochemistry (IHC); soluble MUC1 levels; anti-tumor activity

Key Eligibility Criteria

- Inclusion: Previously treated and incurable malignancy of type reported in literature to express MUC1; age ≤ 70 years; absolute lymphocyte count ≥ 1000 cells/µL and adequate organ function
- Exclusion: Known autoimmune disease, immunodeficiency, or requirement for chronic immunosuppressive therapy

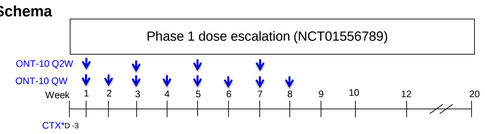
Design: 3+3 dose escalation of ONT-10 at 4 dose levels and 2 administration schedules

- Doses: 250 µg, 500 µg, 1000 µg, 2000 µg (based on M40Tn6 antigen content)
- Schedule 1: Subcutaneous (SC) dosing every 2 weeks (Q2W) for 4 doses
- Schedule 2: SC dosing every week (QW) for 8 doses
- Cyclophosphamide: single dose of 250 mg/m² IV on day -3
- Anti-tumor activity by RECIST 1.1 at baseline, week 9/10, and week 20, and also by irRC (immune-related Response Criteria) at week 9/10 and on maintenance protocol. MUC1 specific humoral response by ELISA and cellular response by IFNγ ELISPOT at baseline, week 5, 9/10, 20, and on maintenance protocol.

Maintenance protocol

- Patients with stable disease (SD) at week 12 and no significant toxicity are eligible to enroll in a separate maintenance protocol to receive ongoing ONT-10 every 6 weeks (Q6W).

Study Schema



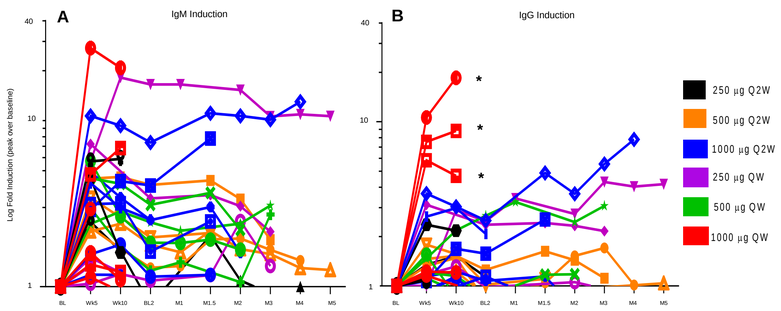
*Cyclophosphamide 250 mg/m² IV on day -3

Induction of Immune Response by ONT-10

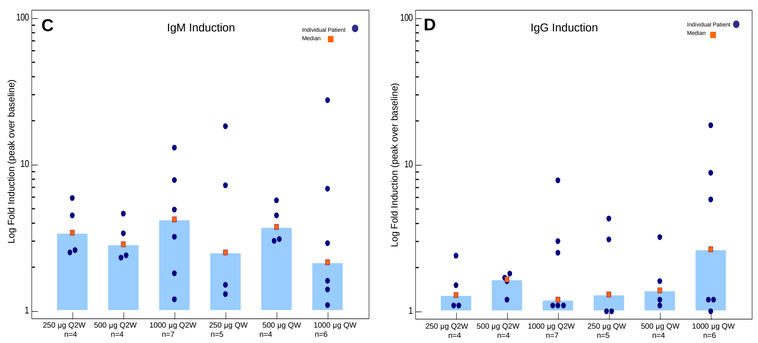
Summary of Overall Immune Response

- **ONT-10 induces both IgM and IgG anti-MUC1 responses in the majority of patients**
- **IgM responses**
  - High induction across all doses and schedules, with mean fold increase from baseline for all patients = 5.1 (range: 1.1-27.4)
  - Many titers exceed 1:50,000 starting at week 5
- **IgG responses**
  - Apparent dose and schedule response
  - Mean fold increase from baseline for all patients = 2.8 (range 1-18.5)
  - For patients receiving 1000 µg QW dose, the mean fold increase from baseline = 6.1 (range 1.1-18.5)
  - 50% (3/6) patients in 1000 µg QW dose with IgG titers ≥ 1:12,800, including 2 patients with titers > 1:50,000
- **Cellular response**
  - T cell response analysis ongoing using IFNγ ELISPOT assay, which is being optimized with *in vitro* stimulation
  - In CD28/CD49d-costimulation ELISPOT assays of samples from three patients with positive IgG responses, 2/3 patients (dosed at 250 µg and 500 µg, respectively), showed a > 2-fold increase in IFNγ from baseline.

ONT-10 Humoral Response



Serum samples were collected at baseline and at scheduled intervals after vaccination with ONT-10. IgM and IgG were measured by ELISA using M40Tn6 peptide-coated plates. Shown is the time course of anti-MUC1 antibody fold induction (peak level over baseline level) for individual patients (solid lines) and for dose and schedule cohorts (colors). **A.** IgM O.D. at 1:800 fold dilution. **B.** IgG O.D. at 1:200 fold dilution. Abbreviations: BL baseline, BL2 maintenance study baseline, M1-5 maintenance study cycle number (Q6W).
***** Later time points pending.

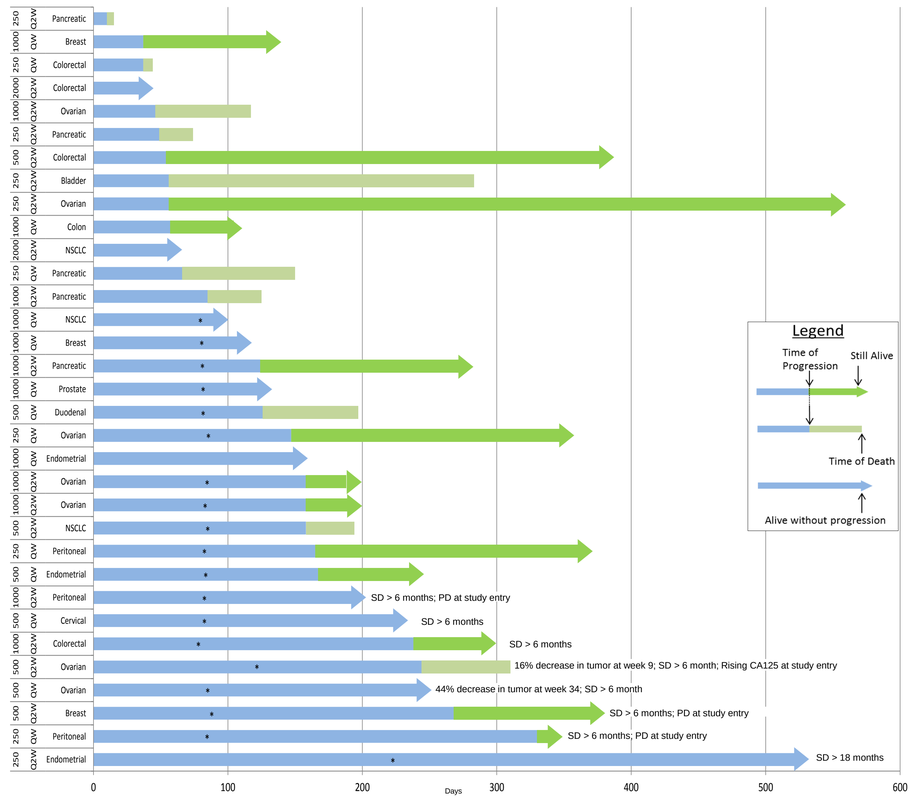


Fold induction of anti-MUC1 antibody for individual patients and the cohort medians (orange square) for each ONT-10 dose and schedule. **C.** IgM. **D.** IgG.

Tumor Response and Disease Control

- **31 patients evaluable for response by RECIST 1.1 criteria or irRC and RECIST 1.1 criteria**
  - Best response by RECIST 1.1 has been SD[1] in 20 patients (65%) and progressive disease (PD) in 11 patients (35%)
- **Decrease in size of tumor lesions (nodal disease) has been seen in two patients**
  - 16% decrease (RECIST 1.1) at week 9 (ovarian cancer, 500 µg Q2W)
  - 44% decrease (irRC) at maintenance cycle 4 (34 weeks from first dose of ONT-10, ovarian cancer, 500 µg QW)
- **8 patients have been progression free for > 6 months (range 6-18)**
  - Diagnoses: Ovarian/primary peritoneal (n=4); endometrial, breast, colon, pancreatic (n=1 each)
  - Median prior lines of therapy: 3 (range: 1-6)
  - Disease growth status at study entry: PD (n=3), SD with rising tumor marker (n=1), SD (n=4)
  - Tumor MUC1 status by IHC (archival samples): 5 positive; 3 unknown
  - Fold induction of anti-MUC1 antibody: IgM (mean 5.9; median 3.1; range 2.3-18.2) and IgG (mean 2.4; median 1.5; range 1.1-7.8)

[1] Includes patients with measureable disease and patients with non-measureable disease without progression (i.e., non-complete response, non-PD).



PFS and overall survival disposition for all patients receiving at least one dose of ONT-10 through cohorts 1000 µg Q2W and 1000 µg QW. The blue bar represents time to progression and a blue arrowhead indicates progression has not yet occurred as of censor date (10/13/2013). The green bar indicates time of survival after progression and a green arrowhead indicates that the patient is still alive as of censor date.
Patient cancer diagnosis and ONT-10 dose and administration schedule are indicated along the y-axis.
* Start of maintenance protocol.

Demographics and Safety

Patient Demographics and Baseline Characteristics

	Q2W				QW				Total
Cohort	1 250 µg	2 500 µg	4 1000 µg	7 2000 µg	3 250 µg	5 500 µg	6 1000 µg	8 2000 µg	
n	5	4	7	2	5	4	6	Enrolling	33
Age*	51	53	64	59	67	64	59		
Sex (M/F)	3/2	1/3	1/6	2/0	0/5	1/3	2/4		10/23
Prior Lines Rx*	2	6	4	1	3	4	3		
Tumor Type									
Ovarian/PP	1	1	4		3	1			10
Pancreatic	2		2		1				5
Endometrial	1				1	1	1		4
Breast		1					2		3
Colorectal		1	1	1			1		4
Lung		1		1			1		3
Other	1					2	1		4

*Median. Abbreviation: primary peritoneal (PP). Other: bladder (1); cervical (1); duodenal (1); prostate (1).

Treatment-Related AEs Reported in > 15% of Patients

	Q2W			QW			Total
	250 µg (N=5)	500 µg (N=4)	1000 µg (N=7)	250 µg (N=5)	500 µg (N=4)	1000 µg (N=6)	(N=31)
Fatigue	4 (80)	1 (25)	2 (29)	1 (20)	2 (50)	0 (0)	10 (32)
Injection site reaction*	0 (0)	1 (25)	1 (14)	2 (40)	2 (50)	0 (0)	6 (19)

* Includes injection site reaction, injection site induration, injection site erythema, and injection site pruritus.

Phase 1 Patient Disposition

	Q2W				QW			Total
Cohort	1 250 µg	2 500 µg	4 1000 µg	7 2000 µg	3 250 µg	5 500 µg	6 1000 µg	
Dose Escalation (n)	5	4	7	2	5	4	6	33
Active	0	0	0	2	0	0	3	5
Completed	1	3	6	NA	3	4	1	18
Discontinued Early*	4	1	1	0	2	0	2	10
Maintenance (n)	1	3	5	NA	3	4	3	19
Active	1	0	1	NA	0	2	3	7
Discontinued**	0	3	4	NA	3	2	0	12

*All early discontinuations due to disease progression with exception of one patient found to have pre-existing hypothyroidism.
**All discontinuations due to disease progression

Summary of Safety

- **ONT-10 has been well tolerated at all doses and schedules through 1000 µg QW and Q2W**
  - No dose-limiting toxicities
  - Greater than 90% of all AEs have been Grade 1/2
  - No Grade 4/5 adverse events
  - No related serious adverse events (AEs)
- **The most common AEs (> 15% of patients) have been fatigue, nausea, abdominal pain, constipation, pyrexia, and bone pain**.
- **The most common treatment-related AEs have been fatigue and injection site reactions**.
  - All treatment related AEs have been Grade 1/2 and all injection site reactions Grade 1

Summary and Conclusions

- **ONT-10 has been well tolerated at doses through 1000 µg administered Q2W or QW over an 8-week period and when administered every 6 weeks as maintenance therapy for up to 11 months.**
- **Consistent with preclinical data, ONT-10 induces IgM and IgG anti-MUC1 response in the majority of patients, with titers frequently exceeding 1: 50,000.**
- **The data support a schedule and dose response, with the greatest IgG response to date occurring at the highest weekly dose tested, 1000 µg QW.**
- **T cell response analysis is ongoing. Preliminary evidence of induction of a T cell response has been seen using CD28/CD49d-costimulation in the ELISPOT assay.**
- **Encouraging disease control has been seen in patients with heavily pretreated and incurable cancers, and greater than 50% of patients have enrolled in the maintenance study.**
- **Consistent with other reports of delayed response to immune therapy, tumor shrinkage has been seen as late as 34 weeks after initiating ONT-10 therapy.**
- **Next steps in ONT-10 development include completion of dose escalation through 2000 µg Q2W and QW, further evaluation of ONT-10 induced T cell response, and potential expansion into disease-specific indications.**

Acknowledgements

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Data are from an unlocked database (safety and survival data cut-off dates September 9 and October 13, 2013, respectively) and are subject to change.