A Phase Ib Study of Indirect Immunization with Oregovomab and TLR3 Stimulation with Hiltonol® in Patients with Recurrent Platinum Resistant Ovarian Cancer (PROC)

Robert W. Holloway, MD¹, Sarah M. Temkin, MD²; Sarah W. Gordon, DO²; Christopher F. Nicodemus, MD³, Madi Madiyalakan, PhD⁴, William P. McGuire, MD²
¹AdventHealth Cancer Institute, Orlando, FL 32804; ²Virginia Commonwealth University, Richmond, VA 23298; ³AIT Strategies, Franconia, NH 03580; ⁴OncoQuest, Inc., Edmonton, AB T6E 6S4, Canada

ABSTRACT: This phase IB study assessed safety of Oregovomab(O) indirect immunization (monoclonal antibody for CA125) and TLR3 stimulation with Hiltonol (polyICLC) in PROC. Secondary endpoints were tumor response, immune response, response to subsequent therapies, and overall survival.

Methods: Patients (pts) with PROC (median 5 prior Rx) received 4 IV infusions with 2 mg oregovomab followed by 2 mg Hiltonol IM 30 min & 48 hrs post the infusion at weeks 0,3,6 and 9. At week 12, imaging was performed & elective chemotherapy was allowed. A final IV oregovomab & IM Hiltonol set was given at wk16 & pts were followed for long term outcomes post the indirect immunization in conjunction with continuing palliative therapies.

Results: 17 pts were enrolled at 2 centers; 15 were dosed and 13 completed the minimum 3 infusions. Treatment phase safety analysis is complete & post IT follow-up is ongoing. Local site reactions to Hiltonol and mild fatigue/flulike symptoms were reported in 13(87%) pts. Serious adverse events were reported in 5(33%) pts, all of these attributed to underlying disease. No new safety signals were observed. Six (40%) had stable disease through the 12 wk immunization period. Four pts with persistent/progressive disease stopped IT prior to infusion 4. Early humoral response by week 6 was observed in 7 of 9 (77%) pts with the available samples. 14 pts took additional cancer Rx. 9 (60%) have died of disease and 6 (40%) continue on palliative therapies.

Conclusion: Optimal use of indirect immunization in this setting likely requires schedule sensitive concomitant administration of the immunotherapy with select antineoplastic therapies analogous to the emerging observations for combination chemo-immunotherapy with oregovomab in the front line setting. This study establishes that Hiltonol is appropriate to include with oregovomab in such future studies.

Background & Rationale: Indirect Immunization is a method to induce antitumor immunity in cancer patients by administering low mg dose of tumor antigen specific antibody to patients in a limited series of infusions. Oregovomab is a CA125 specific antibody that has been most extensively evaluated according to this method primarily in ovarian cancer patients expressing CA125. Efforts to avoid the immune suppression of both tumor burden and treatment with cytotoxic agents failed to demonstrate clinical activity of the maintenance approach, however phase I & II studies with the antibody have demonstrated clinical activity and/or more potent bioactivity in combinatorial settings in treatment of front line and recurrent disease respectively (Braly JIT 2009, Ferrandina ASCO Proceedings 2017, Battaglia 2019 (submitted), and Gordon Gyn Onc 2004) despite the presumed immune suppressive state of these patients.

Current understanding suggests that schedule dependent immune modulatory effects of anticancer therapies may permit enhanced immune response to indirect immunization and suggest that further exploration of immune modulatory combinations is warranted. Hiltonol is a toll like receptor 3 agonist that has been extensively as a cancer immune adjuvant using a variety of tumor vaccination strategies (Butowski J Neurooncol 2009, Caskey J Exp Med 2011) but has not previously been combined with oregovomab or other indirect immunizing antibodies. This study combined the standard dose of both oregovomab, typically being used in ovarian cancer indirect immunization protocols (2 mg IV Q3 to 6 weeks times 4) and the current dose of Hiltonol found to have an optimal immune stimulatory to toxicity profile for evaluation of safety and feasibility in patients with heavily pretreated platinum resistant ovarian cancer and persistent progressive disease. Four immunizations were provided as a mono-immunotherapy through week 12 and then salvage or palliative treatments were permitted with one final indirect immunization at week 16. These advanced progressive disease patients were then to be followed for up to an additional 3 years to assess long term outcomes and track continuing palliative therapies.

Study Variables and Statistical Analysis:	Demographics and clinical characteristics
The Primary Endpoint was Safety:	
Adverse events and clinically significant changes in the subject's physical examination findings, vital signs and clinical laboratory results were evaluated and summarized	
Secondary Exploratory Endpoints:	
<ul style="list-style-type: none">Clinical Response during 12 week immunization (using GCIG/modified irRECIST and RECIST1.1)Response to continuing elective combinatorial therapy post week 12Progression Free SurvivalOverall SurvivalHumoral and Cellular Immune response (Cellular data pending)	

Disposition (of 18 screened)	All Subjects N=15
Entered Study and dosed	15
Received required 3 doses of immunotherapy	13
Age at study entry (years)	
Median	68
Range	42-83
Race & Ethnicity n (%)	
White	12 (80)
Black	1 (6.7)
Other	2 (13.3)
Origin of Epithelial Cancer n (%)	
Ovarian	12 (80.0)
Tubal	1 (6.7)
Peritoneal	1 (6.7)
Other	1 (6.7)
Time since initial Diagnosis (months)	
Median	53.6
Range	25-110
FIGO Stage at most recent recurrence	
I	0 (0)
II	0 (0)
IIIc	10 (66.7)
IV	4 (26.7)
UNK	1 (6.6)
Weight, kg	
Median	78
Range	46-101
Pulse, per minute	
Median	74
Range	52-110
Pre-Immunization CA125, u/ml	
Median	357
Range	63-2140
Lines of Prior therapy	
Median	5
Range	3-8

We thank the patients, their families and study staff corresponding author : robhollowaymd@gmail.com

Study Drug Exposure		Safety Summary	
Parameter		At Least 1 Treatment Emergent Adverse Event	n (%)
Indirect immunizations n(%)	15 (100%)	Relationship	15 (100.0)
Oregovomab infusions		Not Related	n (%)
2	2 (13.3%)	Unlikely Related	n (%)
3	2 (13.3%)	Possibly Related	n (%)
4	3 (20.0%)	Probably Related	n (%)
5	8 (53.3%)	Definitely Related	n (%)
Hiltonol injections		Missing	n (%)
4	2 (13.3%)	CTCAE Grade	
6	2 (13.3%)	Grade 1	n (%)
8	3 (20.0%)	Grade 2	n (%)
10	8 (53.3%)	Grade 3	n (%)
		Grade 4	n (%)
		Grade 5	n (%)
Continuing antineoplastic Therapy:		At Least 1 Treatment-Related TEAE	n (%)
Went to hospice prior to week 12	2 (13.3%)	At Least 1 Grade >=3 TEAE	n (%)
Started chemotherapy & stopped IT	3 (20.0%)	At Least 1 Serious TEAE	n (%)
Started chemotherapy during IT	4 (26.6%)	At Least 1 Treatment-Related Serious TEAE	n (%)
Started chemotherapy post IT	6 (40.0%)	At Least 1 TEAE Leading to Study Withdrawal	n (%)
Went to hospice post week 17	1 (6.7%)		

Treatment Related Adverse Events occurring in 2 or more subjects Grade 3 toxicity all associated with underlying disease

Preferred Term n (%)	Oregovomab (N=15) 11 (73.3)	Hiltonol (N=15) 14 (93.3)
Alanine aminotransferase increased	0	2 (13.3)
Aspartate aminotransferase increased	0	2 (13.3)
Chills	0	4 (26.7)
Diarrhea	2 (13.3)	2 (13.3)
Fatigue	7 (46.7)	6 (40.0)
Influenza like illness	6 (40.0)	6 (40.0)
Injection site discomfort	0	2 (13.3)
Myalgia	0	3 (20.0)
Nausea	5 (33.3)	5 (33.3)
Vomiting	2 (13.3)	0

MedDRA System Organ Class	Statistic	All Subjects (N=15)
Preferred Term	n (%)	7 (46.7)
At Least 1 TEAE with CTCAE Grade >=3		
Gastrointestinal disorders	n (%)	3 (20.0)
Large intestinal obstruction	n (%)	1 (6.7)
Nausea	n (%)	1 (6.7)
Small intestinal obstruction	n (%)	1 (6.7)
Vomiting	n (%)	1 (6.7)
General disorders and administration site conditions	n (%)	2 (13.3)
Asthenia	n (%)	1 (6.7)
Fatigue	n (%)	1 (6.7)
Hepatobiliary disorders	n (%)	1 (6.7)
Bile duct obstruction	n (%)	1 (6.7)
Investigations	n (%)	2 (13.3)
Alanine aminotransferase increased	n (%)	1 (6.7)
Aspartate aminotransferase increased	n (%)	1 (6.7)
Blood alkaline phosphatase increased	n (%)	1 (6.7)
Blood bilirubin increased	n (%)	1 (6.7)
Platelet count decreased	n (%)	1 (6.7)
Metabolism and nutrition disorders	n (%)	2 (13.3)
Dehydration	n (%)	1 (6.7)
Failure to thrive	n (%)	1 (6.7)
Respiratory, thoracic and mediastinal disorders	n (%)	1 (6.7)
Pneumonia	n (%)	1 (6.7)

Discussion and Conclusions
This study established feasibility of adding Hiltonol to Oregovomab as an indirect immunization strategy in PROC. The combination was well tolerated and no unexpected immune treatment safety signals were detected.

Cellular response is pending. Early humoral response to oregovomab was observed in 7 of 9 patients (77.8%) by week 6 suggesting Hiltonol was boosting early immune response to oregovomab infusion with receiving oregovomab analogous to the simultaneous day schedule of chemo-immunotherapy reported by Braly JIT 2009

While this study was ongoing the clinical advantage of chemo-immunotherapy associated with scheduled combination of oregovomab with front line carboplatin-paclitaxel was reported by Ferrandina (ASCO2017)

Patients receiving continuing chemotherapy prior to completion or shortly post immunotherapy exhibited encouraging disease control in association with multiple agents, notably carboplatin, taxanes, olaparib, liposomal doxorubicin, and gemcitabine .

Further exploration of chemo-immunotherapy using indirect immunization with oregovomab with or without Hiltonol in association with simultaneous scheduled administration of these agents is justified.