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Study of autologous dendritic cell therapy targeting mucin 1 as a treatment for the maintenance of ovarian cancer patients in remission

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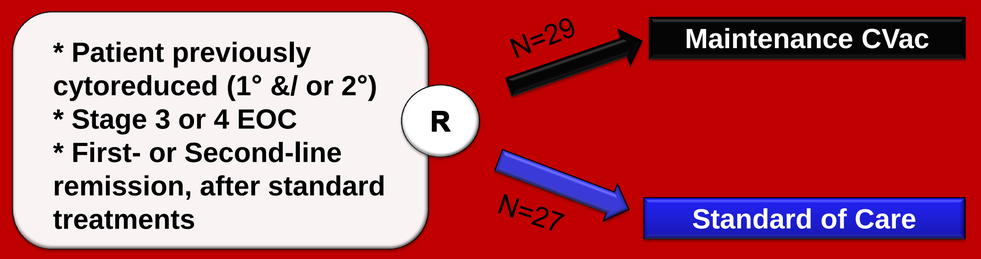
Background: CVac is an autologous cellular therapy targeted to elicit a T cell response to tumors that over-express mucin 1 such as epithelial ovarian cancer (EOC). CAN-003 is a randomized, open-label, Phase 2b trial evaluating the safety and efficacy of CVac given as a single agent to EOC patients who are in complete remission (CR) following first- or second-line chemotherapy.

Design: Patients were eligible if they had stage III or IV EOC and obtained a complete response to standard first- or second-line platinum/ taxane based chemotherapy. The first 7 patients received CVac to allow evaluation of manufacturing in the U.S. and AUS and for safety evaluation. Patients were then randomized either to CVac therapy or standard of care (SOC). Patients in the active group were treated with up to 10 doses of CVac, 4 weekly for 7 doses, and 8 weekly for 3 additional doses.

Efficacy:
Progression Free Survival (PFS) was the primary measure of efficacy. Both first- and second-line responding patients were determined to have progression of disease (PD) on the basis of: 2 serum values of CA-125 ≥ 2× ULN performed at least 1 week apart, regardless of computed tomography (CT) scan results, based on Gynecologic Cancer Intergroup (GCIG) criteria, or increasing clinical or radiological evidence of disease since study entry, regardless of serum CA-125 per Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Safety:
General laboratory values, physical examinations, vital signs, concomitant medications, and Adverse Events (AEs) evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events V4.0.



Demographics:
63 patients were enrolled into the trial. The first 7 patients were not randomized (NR CVac) and the subsequent 56 patients were randomized to either CVac (29 patients) or to SOC (27 patients). Details are tabulated.

Characteristic	CVac (N=29)	SOC (N=27)
Remission Status		
First-line therapy	19 (66%)	17 (63%)
Second-line therapy	10 (34%)	10 (37%)
Disease stage		
III	24 (83%)	20 (74%)
IV	5 (17%)	7 (26%)
Cytoreduction		
Optimal	26 (90%)	21 (78%)
Suboptimal	3 (10%)	6 (22%)
Age (years)		
Mean	56.8 (8.5)	56.2 (9.5)
Median	58.0	55.0
Min, Max	34, 75	40, 74

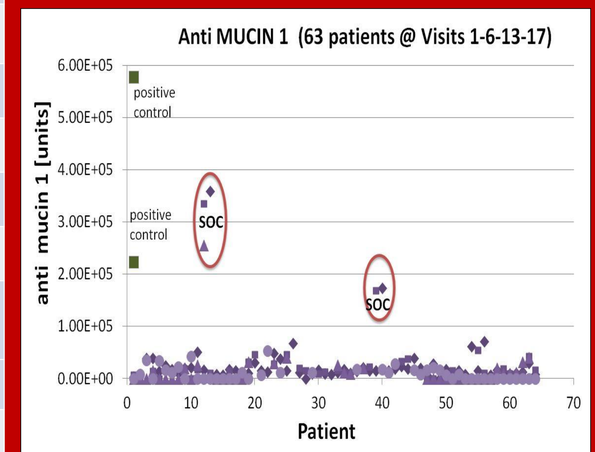
Safety Results:
Results indicate that CVac was generally well tolerated, with no Serious Adverse Events (SAEs) considered related to protocol therapy, and the majority of AEs were considered mild and transient in nature.

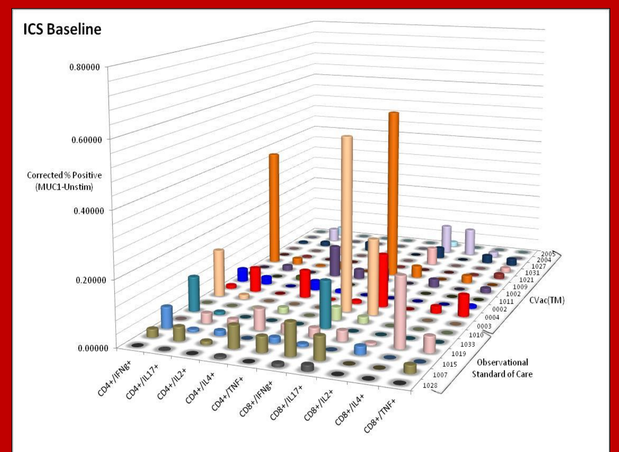
Event	Onset	End	Outcome	Causality
Small bowel obstruction	22 June 2012	30 June 2012	Recovered w/ treatment	Unlikely Related
Abdominal pain, dehydration, nausea, vomiting	25 June 2011	29 June 2011	Recovered w/ treatment	Not Related (NR)
Abdominal pain	20 Aug 2011	22 Aug 2011	Recovered	NR
Respiratory failure	21 Aug 2011	27 Aug 2011	Fatal	NR
Small bowel obstruction	28 Sept 2011	8 Oct 2011	Recovered	NR
Febrile neutropenia	24 Nov 2011	29 Nov 2011	Recovered	NR
Surgical removal iliac node (hospitalization for disease progression)	16 Dec 2011	19 Dec 2011	Recovered w/ treatment	NR
Small bowel obstruction	5 Nov 2012	8 Nov 2012	Recovered	NR
Disease progression	22 July 2013	25 July 2013	Ongoing	NR

Immune Monitoring Results:
No humoral immune response was induced by CVac. A mucin 1-specific, cellular immune response was observed by Intracellular Cytokine Staining (ICS) of T cells from peripheral blood mononuclear cells (PBMCs). Because of the large variability across patients, statistical analyses of the ICS data were performed across the treatment window, looking for the most enriched responses. Patients treated with CVac were assessed based on the maximum post-baseline response, to enable overall signal detection, rather than focusing on average. Preliminary data is tabulated.

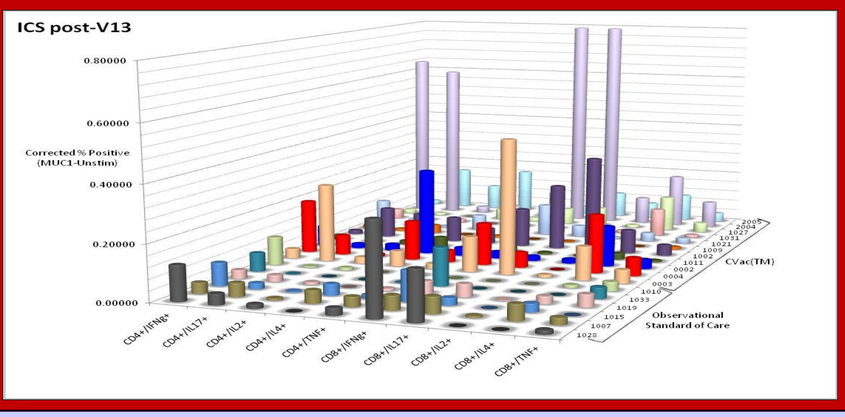
	CD4 IL-2	CD4 IL-4	CD4 IFNg	CD4 TNFa	CD4 IL-17
CR1	*	*	*		
CR2	**	**	*		
CR1 + CR2					
	CD8 IL-2	CD8 IL-4	CD8 IFNg	CD8 TNFa	CD8 IL-17
CR1	*	**		**	
CR2		*		*	**
CR1 + CR2		*	*		*

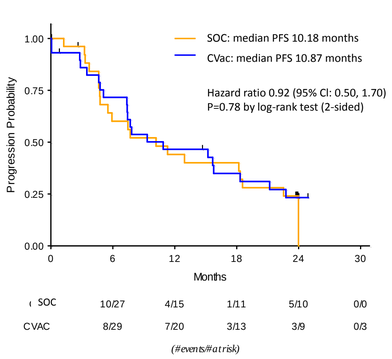
* $p \leq 0.10$ ** $p \leq 0.05$



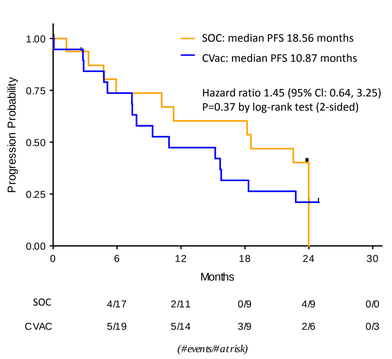


Efficacy Results:
Although this study was not adequately powered, the Kaplan-Meier estimate of median PFS (ITT population) resulted in no observed difference between the treatment groups; a median PFS of 10.18 months was observed in the SOC group (n=27) as compared to 10.87 months in the CVac treated (n=29), (HR 0.91, p=0.78 (95% CI: 0.49, 1.71)). The median PFS was also estimated for the individual strata of patients in either first or second remission. These data resulted in an unexpected finding in patients who were in first remission where the median PFS strongly favored the SOC arm (18.56 months) when compared to the CVac treated patients (10.87 months), (HR 1.45, p=0.37 (95% CI: 0.64, 3.25)). Importantly, a favorable trend was observed in patients in second remission when treated with CVac, with a median PFS of 7.69 months as compared to patients on the SOC arm of 5.14 months (HR 0.41, p=0.09 (95% CI: 0.14, 1.21)). Regarding the overall survival, 8 patients have been confirmed to decease to date and we'll continue to monitor the overall survival signals in the trial.

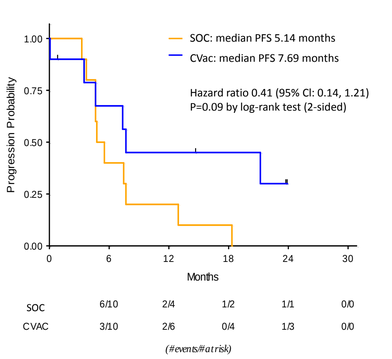




Kaplan-Meier Analysis of PFS in Patients after Chemotherapy (ITT Population)



Kaplan-Meier Analysis of PFS in Patients after First -Line Chemotherapy (ITT Population)



Kaplan-Meier Analysis of PFS in Patients after Second-Line Chemotherapy (ITT Population)

CONCLUSION:
CVac was well tolerated and non-toxic. In terms of immune activity, CVac induced a mucin 1-specific T cell response and did not induce a mucin 1-antibody response. For the overall population, there was no apparent difference between the treatment arms for PFS. However, divergent trends were observed between first- and second-line remission groups; although the patient numbers were small in each group. Regarding overall survival, 8 patients have been confirmed to be deceased to date; overall survival will continue to be monitored in the trial.

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