Phase IIa Trial of the Intraperitoneal Implantation of Agarose-Agarose Macrobeads Containing Mouse Renal Adenocarcinoma Cells in the Treatment of Advanced Stage, Treatment-Resistant Metastatic Colorectal Cancer:
LDH as a Biomarker of Response and Overall Survival

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BACKGROUND: Cancer is a systems biology disease. Accordingly, the use of cell systems with the ability to modulate the multiple, complex mechanisms responsible for tumor progression and metastasis appears merited. We report here the results of a Phase IIa clinical trial of bilayer agarose macrobeads containing mouse renal adenocarcinoma cells (RENCA macrobeads) in the treatment of advanced, multiple–prior-therapy, treatment-resistant metastatic colorectal cancer (IND# BB-10091). Th RENCA macrobeads produce and release factors from colonies composed of cells with cancer stem cell properties and their daughters that induce changes in multiple gene families, the net result of which is suppression of freely-growing animal and human cancer cells *in vitro* and *in vivo* and prolonged survival in animals with spontaneous or induced tumors (**Cancer Res** 71(3): 725-35, 2011). Reported here is the evaluation of the usefulness of lactic acid dehydrogenase (LDH) as a biomarker predictive of overall survival.

METHODS: Thirty-four patients who had failed all available treatments with advanced mCRC and limited life expectancy underwent intraperitoneal implantation of RENCA macrobeads (8 per kg body weight) up to a maximum of four implants via laparoscopy under general anesthesia in this open-label, single-arm trial. Serial physical examinations, lab profiles (including tumor markers (CEA, CA19-9), inflammation markers, LDH, liver profile, among others), and PET-CT imaging to measure number/volume and metabolic activity of the tumors were done pre- and three months after each implant to assess safety and efficacy (tumor marker decrease, response on imaging, and overall survival (OS)).

RESULTS: Two groups of patients: i.e., Responders (R, n=25) and Non-Responders (NR, n=9), were defined by the patterns of their LDH values at Days 30 and 60 after their first macrobead implantation. The two groups were not distinguishable by their baseline mean or median LDH values (R, mean 290.40+/-325.08 vs. NR, 382.78+/-350.78; t-test, p=0.4789), whereas at Day 30, mean R LDH value was 305.92+/-284.76 vs. NR, 649.33+/-363.60; $p \leq 0.0070$. The R and NR groups were also statistically different with respect to their mean LDH levels at Day 60: R, 333.88+/-445.89 vs. NR, 1278.50+/-761.94; $p \leq 0.0001$. These results correlated with the number of implants subsequently received and also overall survival, with a mean difference between R and NR of at least three months. Tumor marker results for both CEA and CA19-9 were less reliable markers than LDH, with CEA in particular being subject to the effects of systemic inflammation.

CONCLUSION: The evidence presented here indicates that the RENCA macrobeads have an anti-tumor effect that is seen in 25 of the 34 patients (73%) in this open Phase IIa trial in mCRC patients. This effect appears to offer preliminary support to the hypothesis that cell system therapy can be effective as a therapeutic modality. In addition, LDH appears to be a predictive and reliable marker of response after macrobead implantation. Further studies of efficacy and the value of LDH as a biomarker in larger numbers of patients are merited and currently ongoing in a multi-site Phase IIb trial.