TAG Vaccine Clinical Trial Manufacturing

Phillip B. Maples[1], Padmasini Kumar[1], Yang Yu[1], Beena O. Pappen[1], Joseph Kuhn[2] and John Nemunaitis[1, 3, 4, 5]

[1]Gradalis, Inc., Dallas, TX; [2] General and Oncology Surgery Associates, Dallas, TX, [3] Mary Crowley Cancer Research Centers, Dallas, TX; [4]Baylor Sammons Cancer Center, Dallas, TX; [5]Texas Oncology, P.A., Dallas, TX

Gene modified cell-based cancer vaccines have demonstrated durable response in selected patients. We have developed the novel nonviral TAG expression vector that we believe, when transfected into tumor cells, will evoke immune recognition /stimulation by two distinct routes. TAG vaccines express both GM-CSF and a TGFβ_2 antisense (P. Kumar, et al., BioProcessing J.8(1):30-36 and Maples, P, et al., BioProcessing J. 8(1):38-45, 2009). Our Phase I clinical protocol (n=55 patients) was opened in May, 2008 (BB-IND 13650). Advanced cancer patients that have sufficient accessible tumor tissue are eligible for trial entry. Thirty eight patients have been consented for vaccine manufacturing. Tumor types collected include colorectal (8), NSCLC (8), breast (4) and melanoma (5). Of the 31 successful manufacturing processes released to date, 11 patients' vaccines are in the low dose cohort ($1x10^7$ cells per dose) and 20 patients' vaccines are in the high dose cohort ($2.5x10^7$ cells per dose). There were 6 manufacturing failures, due to insufficient starting material (3) or contamination (3). The contaminations occurred with tumor tissue procured from the GI tract. We no longer harvest tumor for vaccine manufacturing from the visceral lumenal area. Product stability has been monitored over one year by sterility, GM-CSF mRNA and TGFβ_2 antisense expression and other parameters. Average cell viability is 91.9$\pm$5.6%, median 94% and range 76-98% (values taken on Day 2 of manufacturing). After each patient vaccine is manufactured, GM-CSF, TGFβ_1 and TGFβ_2 protein expression are assessed by immunoassay comparing transfected and nontransfected tumor cell expression over 14 days. Average GM-CSF expression is 823$\pm$1376pg/$1x10^6$ cells/ml, median 230pg and range 7-5071pg. The mean pretransfection TGFβ_1 is 3225$\pm$2941pg/$1x10^6$ cells/ml, median 2950pg. The mean posttransfection TGFβ_1 is 2964$\pm$2644pg/$1x10^6$ cells/ml, median 2550pg. The average percent knockdown of TGFβ_1 was -32$\pm$160%, median 6% and range -833-(+97)%. The mean pretransfection TGFβ_2 is 784$\pm$1118pg/$1x10^6$ cells/ml, median 385pg. The mean posttransfection TGFβ_2 is 203$\pm$198pg/$1x10^6$ cells/ml, median 150pg. The average percent knockdown of TGFβ_2 was 52$\pm$39 %, median 45% and range -8-(+100)%. In all but two instances, GM-CSF secretion met our product release specification. TGFβ_2 knockdown was evident in all vaccines although in 4 instances it did not reach our 30% knockdown goal. TGFβ_1 expression was assessed pre and post transfection (no effect) and TGFβ_1 levels were typically much higher than TGFβ_2 levels. TGFβ_1 is thought to be the more dominant immunosuppressive agent in many cancers and these data underscore its presence in these tumors and vaccine products.