Stat Analysis plan

Title: ZOSTAVAX in Persons Imminently Receiving Chemotherapy for Solid Organ Tumors

NCT02444936

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2.7 Statistical Analysis and Sample Size Justification

This study is a pilot protocol. Our goal is to enroll a total of 90 subjects (30 Duke, 60 Cleveland).

For the primary analysis: If we anticipate a loss of up to 15% of subjects for various reasons beyond our control so that we will end up with about 76 subjects for full analysis. Using G*Power to perform a sample size calculation with 76 subjects (38 vaccinated and 38 un-vaccinated) and an analysis comparing these two groups at the 3 time points to test Hypothesis 1 using a 2 x 3 Repeated Measures ANOVA with power 0.8 and α error 0.05 we can detect an effect size of 0.27. For independent t-tests analyzing mean differences at each individual time point we would be able to detect an effect size of 0.58. For both of these types of analyses our power is near a medium effect size. We do not have preliminary data in this population for a precise sample size calculation. The data from this pilot study will inform the sample size for a larger future study.

Fold change will be the primary immune analysis and will be calculated for each individual subject based on their day 0 SFU on ELISPOT. Fold change will be calculated at each time point (chemo initiation, during chemo, 3 months post). This will take place in both the vaccinated and non-vaccinated groups. As this model reflects a 2 group by 3 time point design, our initial overall assessment of the data will use a 2X3 Repeated Measures ANOVA (RMANOVA) to identify mean differences between groups, within time mean differences, and the interaction between groups and time to identify if the trends in the means over time is different for groups (vaccine vs. no vaccine). For the next step to gain a better understanding of how well the vaccine works at each time point (Hypothesis 2-4), we will use independent samples t-tests to analyze group mean differences at each time point separately to gain a better understanding of how the groups may be different at chemotherapy initiation, during chemotherapy, and at 3 months post-chemotherapy. Additionally, if we identify a significant interaction between group and time points, we will run follow-up RMANOVAs for each group separately to identify not only mean difference over time, but also linear (e.g. a steady increase or decrease in mean scores over time) and quadratic (e.g. a high mean scores at chemotherapy initiation, followed by a decline in mean score during chemotherapy, followed by a steady increase in mean score at 3 months post-chemotherapy) trends in the means over time for each group. Violations of the assumptions for each analysis will be tested and the data will be transformed or the nonparametric equivalence analysis will be used when appropriate.

Dr. Christopher Burant is the director of the Cleveland VA's core statistical center. He is an ongoing Co-investigator with effort on one of Dr. Canaday's R01 grants. He will perform the statistics for this study.

Safety and tolerability will be assessed by statistical and clinical review of all safety data collected throughout the study. All subjects who are vaccinated and provide any safety follow-up will be included in safety analyses and summaries. To provide an overall assessment, the incidence rate for the vaccination group and no-vaccination group, the risk difference between the two groups and the associated 95% CI will be provided for broader safety measures such as the proportions of the subjects with any: adverse experiences; injection-site adverse experiences; systemic adverse experiences; serious adverse experiences; or vaccine-related serious adverse experiences after vaccination.