Cover page

Mitigation of radiation pneumonitis and fibrosis

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Statistical methods plan

Power analysis for aim 1
For the RP endpoint, at an 11% rate of clinical RP, and an 80% mitigation effect, 97 subjects are needed per arm for type 1 error of 0.05 and a power of 0.80. The 11% and 80% figures are based on our retrospective studies. Only 49 are needed per arm for a baseline clinical RP rate of 20%. We plan for 200 subjects because there is variability in the rate of RP, and because we cannot be certain about the magnitude of efficacy of enalapril.

control	%difference	treatment	n/arm	total n
11%	50%	6%	306	612
11%	60%	4%	199	398
11%	70%	3%	136	272
11%	80%	2%	97	194
11%	90%	1%	70	140
20%	50%	10%	155	310
20%	60%	8%	101	202
20%	70%	6%	70	140
20%	80%	4%	49	98
20%	90%	2%	36	72

For a 50% radiographic rate of RP, and a halving of this by enalapril, 45 subjects are needed per arm.

50%	50%	25%	45	90
50%	60%	20%	30	60
50%	70%	15%	21	42
50%	80%	10%	15	30
50%	90%	5%	11	22

For the radiographic fibrosis endpoint, at a 90% fibrosis rate, 29 subjects per arm would identify a 30% reduction in radiographic fibrosis at 6 or 12 months.

Endpoint and RAS analyses

Dichotomous variables will be compared by chi-square, or Fisher's exact test, as indicated. Continuous variables will be compared by parametric or non-parametric statistics, as appropriate. Repeated measurements on the effects of enalapril and placebo on [RAS components] will be tested by a repeated measures ANOVA for continuous [RAS component] values and by a logistic type regression models [using GEE techniques for discrete [RAS component] values. In either case appropriate generalized linear models
methods will be used to account for the association between repeated measurements over time on the testing procedure.] We will repeat the analysis using an appropriate regression analysis to account for possible patient factors which may influence outcome in addition to enalapril. We will also look at a model for RP and fibrosis using enalapril use and the RAS components as predictors as well as interactions between drug use and these predictors. Correlations will be made using Spearman's or Kendall correlation, as indicated. Dose modification factors (DMF) for the use of enalapril compared to placebo will not be tested since the expected radiation dose ranges will be too narrow. A more formal attempt to understand the mechanism of enalapril action on RP and fibrosis and determine if this is possibly derived through any one of the [RAS components] will use a structural equation modeling approach. This approach uses a matrix of regression coefficients from a series of regression models [of intermediate effects at the various time points to other intermediate effects at the same time point or to future intermediate or terminal effects. Using these coefficients and a postulated causal diagram which depicts which effects may be dependent on the patient history at a given time]. A final causal diagram which shows the relationship between drug, intermediate outcome and RP and or fibrosis [is constructed]. Path analysis techniques to construct the causal diagram can be constructed using the program DIGRAM (53). [This cited reference shows how this approach works by looking at causal factors for heart disease using data on behavioral factors measured at epochs in time.]

Survival analysis for aim 3

Cancer-related survival and cancer recurrence will be compared for the enalapril and the placebo groups using Kaplan-Meier statistics. [We have calculated our ability to detect significant changes in cancer recurrence rates and in cancer survival, both for improvements in cancer-related outcomes and for adverse trends. We will be able to detect significant increases in recurrence rates or mortality. Our cohort of 162 subjects showed no difference in patient survival for those on ACE inhibitor compared to those not on ACE inhibitor. We do not

expect adverse changes in recurrence rates or patient survival. A mitigation benefit by enalapril could lead to an increase in patient survival, but less than a three month increase is not likely to be detected]

Recurrence rate change	*Percent chance of detection*
40 to 20 %	80%
40 to 60 %	81%

Cancer median survival change, months	*Percent chance of detection*
18 to 21	11%
18 to 12	60%

[There are potential pitfalls in the recurrence and survival analyses. These include the effects of interim sampling for the safety analyses, and adjustments for patient and disease characteristics as well as missing data.] The interim masked safety analyses will use the O'Brien correction to take into account the multiple analyses. In our analysis of survival, we will compare the recurrence-free survival rates between the treatment arms of the study in two ways. First we will examine the rates of death or recurrence using a Cox model. In this model we will adjust for patient/disease characteristics such as site of treatment, gender, age, stage of disease at randomization, and radiation dosage. We will also compare the disease free survival probabilities at two years using techniques that we have published (52).This method allows us to deal with the partial information available in patients who do not have a potential follow-up time of two years. This approach, which is a censored data version of logistic regression, will allow us to adjust the comparisons for patient, disease, and treatment factors. We picked two years here since the empirical evidence is that the disease-free survival curves tend to flatten out at around 20 months.