Novel Mechanisms and Predictors of VEGF Receptor Inhibitor- or Immune Checkpoint Inhibitor-Associated Hypertension and Cardiovascular Disease

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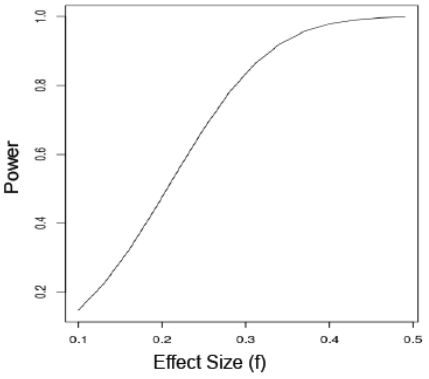
Sample Size and Power Calculation:

Hypertension: In studies of TKI use, increases in blood pressure begin within days and reach steady state over weeks. Pazopanib has been shown to increase mean arterial blood pressure by 15 mm Hg in this time frame[75,76]. Based on the previous studies, we assume it is reasonable to expect the mean changes of BP for placebo group is 15 mm Hg, the mean changes of BP for bosentan group is 7 mm Hg, the mean changes of BP for the ambrisentan group is 0 mm Hg, all with a standard deviation of 10 mm Hg. We first conducted power analysis with ANOVA framework. We planned to recruit 45 patients per group. In power calculation, to account for potential loss-to-follow issue that happens in almost every longitudinal studies, we considered 40 patients per group. With 40 subjects per group, we will have 100% power to detect whether there is any significant differences among three study arms. When comparing ambrisentan group to the placebo, with 40 subjects per group, we will have 100% power to detect whether there is significant difference between two groups. To be conservative, we set the mean changes of BP for placebo group to 12 mm Hg, the mean changes of BP for bosentan group to 6mm Hg. The analysis showed we still have 99.8% power to detect whether there is significant difference between groups.

We also evaluated the required minimum detectable effect size with 40 subjects per group to achieve 80% power. As can be seen from Figure 8, the minimum detectable effect size (f) required is about 0.29 (i.e., 7.7% of the total variance accounted for by groups). Although this is considered a medium effect size (f=0.25, Cohen, 1988), it is much smaller than the effect size we expected (f=0.61).

Figure 8. Effect size vs. power

Effect Size	Power
0.1	0.15
0.13	0.22
0.16	0.32
0.19	0.44
0.22	0.56
0.25	0.68
0.28	0.78
0.31	0.86
0.34	0.92
0.37	0.96
0.4	0.98
0.43	0.99
0.46	1.0
0.48	1.0



When comparing bosentan group to the placebo, with 40 subjects per group, we will have 86.8% power to detect whether there is significant difference between two groups. Significant level was set at 0.05/3 to account for multiple comparison. Once again, we evaluated the required minimum detectable effect size with 40 subjects per group to achieve 80% power. The results showed that the required minimum detectable effect size is d=0.74, which means the minimum detectable difference between placebo and bosentan group is 7.4. Although this is considered a large effect size (d=0.8, Cohen, 1988), we are confident in observing this difference based on previous studies.

Our power analysis is conservative because first the standard deviation of BP changes in placebo group should be much less than 10 mm Hg; Second, the power achieved in analysis of covariance (ANCOVA) is higher than that in ANOVA because the residual variance in ANCOVA is minimized.

FMD: In studies of VEGFR-TKI inhibitors, worsening in endothelial function is proportionate to the increase in blood pressure. Based on our previous work, we anticipate a 3%±4% decrease in brachial artery FMD in subjects treated with placebo[44]. Bosentan has previously been shown to improve endothelial function in hypertension[77], and we anticipate greater vascular function effects with ambrisentan. Like blood pressure outcome, we evaluated the required minimum detectable effect size with 40 subjects per group to achieve 80% power. Once again, as can be seen from Figure 8, the minimum detectable effect size (f) required is about 0.29.This is considered a medium effect size (f=0.25, Cohen, 1988) and we are confident in observing this effect size for FMD outcome based on previous studies.

Data Analysis Plan: We will use standard graphing and screening techniques to detect outliers and to ensure data accuracy. We will assess continuous outcomes for normality. If normality is violated, we will apply data transformation or consider non-parametric analysis methods. We will provide summary statistics for both numerical and categorical variables by study arms. We will assess comparability among randomization groups. Descriptive statistics for the study population, including means, medians, standard deviations, 25th percentile and 75th percentile for continuous variables as well as counts and percentages for dichotomous variables will be reported. Non-parametric Kruskal–Wallis tests will be conducted for continuous variables and Pearson Chi-square tests will be conducted for categorical variables to assess the comparability of demographic and clinical characteristics by study arms.

We will conduct analysis of covariance (ANCOVA), which answers the question whether the BP changes (or

the BP levels at the 4th week), partialling out BP levels at baseline, is different between study arms. Other covariates, such as age, gender, demographic characteristics will also be adjusted in the ANCOVA model. The regression coefficient of study arms and corresponding 95% confidence intervals (CI) will be presented and can be interpreted as the group difference on BP changes, after holding baseline BP and other covariates equal across groups. In additional to adjust linear relationship between the covariates and BP, we will employ a restricted cubic spline for continuous covariates to examine nonlinear relationship, which will provide more precise estimates for group effects. The number of knots was set at 3 because of the small sample size in the current study. We will also explore group by baseline BP levels interactions to examine whether the group effects vary by baseline BP levels. We expect minimal missing data due to the short follow-up for the study.

Bibliography/References

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