COVER PAGE

Official Title: A Study Evaluating a Proprietary Amino Acid Mixture (Enterade®) in Patients Receiving High-Dose Melphalan Conditioning Followed by Autologous Stem Cell Transplantation for Multiple Myeloma and Non-Hodgkin Lymphoma

NCT record number NCT02919670

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13. STATISTICAL CONSIDERATIONS

This is a randomized, double-blinded phase 2 trial of comparing the efficacy of the investigationaldrug, Enterade® versus placebo in conjunction with standard-of-care (SOC) in decreasing diarrhea relatedgastrointestinal (GI) toxicity in patients undergoing autologous hematopoietic stem cell transplantation (HSCT) with melphalan conditioning for Multiple Myeloma or non-Hodgkin Lymphoma.

13.1 Study Design/Endpoints

The study is a one stage phase II trial with two arms. The primary endpoint is the incidence of NCI-CTCAE 4.0 grade 3 or higher diarrhea GI toxicity in the 14 days following autologous HSCT. The primary endpoint will be evaluated at day 14 after autologous HSCT. A total of 114 patients (57 patients per arm) will be randomly assigned in 1:1 ratio to either the investigational drug (Arm A) or placebo (Arm B) prior to autologous HSCT.

Based on the preliminary data with SOC alone, we hypothesize that the grade 3 or higher diarrhea GI toxicity will be 30% in the placebo arm. With the investigational drug, we project that the grade 3 or diarrhea higher GI toxicity will be 10% . With the sample size 57 per arm, there will be 80% power to detect a 20% difference in grade 3 or higher diarrhea GI toxicity between two arms. This power calculation is based on Fisher's exact test at one-sided type I error rate of 0.05.

13.2 Accrual Rate and Study Duration

Based on the current practice, we conservatively anticipate that the accrual rate will be approximately 12 patients per month and thus the accrual will complete within one year. The projected accrual targets presented below is based on patients at DFCI who underwent autologous HSCT for Multiple Myeloma or Non-Hodgkin Lymphoma between 2013 and 2014. In the year 2013, 274 patients underwent autologous transplantation for Multiple Myeloma (182 patients) or Non-Hodgkin's Lymphoma (92 patients). The following year, 159 patients underwent autologous transplantation for Multiple Myeloma and 81 for Non-Hodgkin's Lymphoma, accounting for a total of 240 patients. We anticipate recruitment of approximately sixty percent of eligible patients.

Accrual Targets

Ethnic Category

Sex/Gender

Females Males Total

Hispanic or Latino 2 + 4 = 6

Not Hispanic or Latino 50 + 58 = 108

Ethnic Category:

Total of all subjects

(52) + (62) = (114)

Racial Category

American Indian or Alaskan

Native + 1 = 1

Asian 1 + 1 = 2

Black or African American 2 + 3 = 5

Native Hawaiian or other Pacific

Islander + 1 = 1

White 49 + 56 = 105

Racial Category:

Total of all subjects

(52) + (62) = (114)

13.3 Randomization/Stratification Factors

After enrollment, patients will be randomized in 1:1 ratio between two arms using permuted block algorithm within strata. Randomization will be stratified based on diagnosis of Non-Hodgkin Lymphoma or Multiple Myeloma prior to transplantation. No additional interim monitoring will be performed that is unique to each stratum. Efficacy determination will be the same for each stratum as noted in the primary and secondary endpoints outlined in section 1.2 and 1.3.

13.4 Interim Monitoring Plan

All adverse events will be monitored closely. Monitoring of key safety endpoints (GI toxicity, fever, neutropenia) will be conducted in accordance with the DF/HCC DSMB meeting (see Section 12.2). The investigational drug is a medical food composed of an amino acid mixture and generally recognized as safe constituents. We thus do not anticipate any toxicity or potential risks. However,

taking the advantage of a randomized trial with a standard treatment arm, we will compare all grade 2 or higher treatment related toxicity in accordance with the DSMB meeting.

If, at any of these looks, this difference is significant at the two-sided level of 0.05, this would trigger a consultation with the DF/HCC DSMB for additional review. However, this will not be formal stopping rules that would mandate automatic closure of study enrollment. In addition, we will assess the feasibility of the trial at the first look. With the anticipated accrual rate, we project 2-3 looks before the completion of the accrual.

13.5 Analysis of Primary and Secondary Endpoints

The primary analysis will be the modified intention-to-treat (ITT) analysis for the primary endpoint of grade 3 or higher diarrhea GI toxicity occurred within 14 days of autologous HSCT. Although it is unlikely to occur, patients who are randomized but do not receive autologous HSCT or do not receive any study drug will be replaced and not be included in the primary or secondary analysis. The proportion of grade 3 or higher GI toxicity in the 14 days following autologous HSCT will be compared using Fisher's exact test.

Secondary endpoints as listed in Section 1.3 include frequency and duration of fever and neutropenia, average total daily stool volume, average daily stool frequency, change in weight, calorie consumption, stool microbiome, total use of anti-diarrheal medications, use of antibiotic medications, tolerability, patient reported quality of life (QOL), and the length of hospital stay. Correlative studies include assessment of cytokine levels, fecal lactoferrin, and markers of nutrition and inflammation. For group comparison, Fisher's exact test or a Chi-square test, as appropriate, will be used for categorical variables and Wilcoxon-Rank-Sum or t-test, as appropriate, will be used for continuous variables. In addition, correlation analysis between the primary and secondary endpoints will be performed and multivariable linear regression and logistic regression analysis will be explored to identify factors that are associated with the primary outcome and to identify a subset patients who develop grade 3 or higher GI toxicity. For the analysis of pre-to-post treatment change, graphical assessments, McNamer's test or Wilcoxon-Signed rank test as appropriate, and regression analysis will be utilized.

As to the assessment of patient reported QOL, we project that 70% of all randomized patients will agree to participate in the QOL assessment. This projection is based previous QOL

assessment in the HSCT setting. In particular, we are interested in the overall Epic bowl domain score whether this score is higher in the Enterade arm compared with the placebo arm (the higher score the better). For example, if the effect size of epic bowel domain score (i.e., mean difference between two groups divided by its standard deviation) is 0.7, there will be 86% power to detect this difference. If the effect size is 0.8, then there will be 94% power to detect this difference. This power calculation is based on asymptotic power of the Wilcoxon-Rank-Sum test at the two sided significance level of 0.05 without adjustment for multiple comparisons and assuming the sample size 40 in each arm. As to the missing items in each QOL assessment, we will take a standard approach to handling individual missing items that are received. That is, if an item is missing, the subscale score will be prorated by multiplying the sum of the subscale by the number of items in the subscale and then dividing by the number of items actually answered.

Although we hypothesize that Enterade in combination with SOC will help stabilize small bowel environment, since there have been no rigorous comparative studies performed, all secondary endpoints will be evaluated in an exploratory analysis to characterize the GI response to chemotherapeutic conditioning for autologous HSCT and thus will serve hypothesis-generating purpose for future clinical/scientific research. For this reason, provision of power statement is limited for secondary endpoints.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All participants who receive any amount of study drug will be evaluable for toxicity from the time of their first treatment.

13.6.2 Evaluation of the Primary Efficacy Endpoint

Analyses will be modified intent-to-treat per Section 13.5. All eligible participants who receive the study treatment in the study will be assessed for response/outcome to therapy, even if there are major protocol therapy deviations.