NCT02489448 Neoadjuvant MEDI4736 Concomitant With Weekly Nab-paclitaxel and Dose-dense AC for Stage I-III Triple Negative Breast Cancer

SAP

Date: 2/26/2021

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to AstraZeneca/MedImmune Patient Safety or designee after outcome.

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to AstraZeneca/MedImmune Patient Safety or designee using the Safety Fax Notification Form. The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

All patients enrolled in the Phase I portion of the trial will comprise the safety analysis set to determine the RP2D.

Toxicities will also be reported as descriptive statistics for all patients who received MEDI3476 at the RP2D dose in the Phase I and Phase II portions of the study.

Acute toxicities observed while on treatment will be reported separately from late toxicities that are observed during the 90-day post-treatment follow-up period. Acute toxicities will also be reported separately for the combination with nab-paclitaxel and with ddAC.

11.1.2 Efficacy analysis set

The primary efficacy analysis will include all patients who received at least 12 weeks (i.e. 6 courses) of MEDI4736 therapy at the RP2D.

A secondary, intent to treat, efficacy analysis will include all patients who received at least one dose of MEDI4736 at RP2D.

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

MTD/RP2D determination

In the Phase I safety portion of the trial 2 dose levels will be assessed including 3mg/kg and 10mg/kg concomitant with weekly Nab-paclitaxel and concomitantly with dose dense doxorubicin and cyclophosphamide. Intra-patient dose escalation is not allowed. Dose limiting toxicities will be assessed over the entire 20 weeks of therapy with MEDI4736 to determine MTD/RP2D but will be monitored separately during the two parts of the chemotherapy regimen (nab-paclitaxel x 12 weeks and AC x 4 treatments every two-weeks). Delayed toxicities (i.e. toxicity in the 90 day follow-up period after completion of neoadjuvant therapy) are not considered for DLT purposes.

Analysis of safety endpoint

Interim safety analysis of the Phase II portion of the trial will be performed when 22 patients are accrued who received at least one treatment with MEDI4736. If > 2/22 patients experience DLT or a serious treatment related adverse event (SAE), the MEDI4736 dose schedule will be re-evaluated. If futility criteria is not met at the interim efficacy analysis, the trial will continue after the MEDI4736 dose and schedule is amended to improve safety. With 22 patients in the first stage, there is $\geq$ 90% chance of observing at least 1 DLT event, if the true underlying rate of the adverse event is $\geq$ 10%.

Final toxicity results will be reported as frequency statistics with 95% confidence intervals. All patients who received at last one dose of MEDI4736 at the RP2D will be included in the final toxicity analysis. Acute toxicities that occur during the treatment phase will be reported separately from late toxicities that are encountered during the 90-day follow up period after completion of all neoadjuvant therapy. Acute toxicities will also be reported separately for the combination with nab-paclitaxel and dose dense AC.

Phase I safety portion of the trial

Two dose levels will be assessed including 3mg/kg and 10mg/kg MEDI4736 in combination with weekly nab-paclitaxel x 12 treatments followed by MEDI4736 in combination with ddAC x 4 treatments.

APPROVED BY THE YALE UNIVERSITY IRB 2/26/2021

3 mg/kg MEDI4736 dose level

The first 3 patients will be enrolled at dose level of 3 mg/kg MEDI4736 concomitant with chemotherapy. Further accrual will be halted after the first 3 patients are enrolled until the DLT assessment is complete for a given treatment part of the two-part (weekly nab-paclitaxel x 12 + AC x 4) chemotherapy regimen. If no patients experience a DLT during the weekly nab-paclitaxel treatment period (12 weeks), the next 3 patients will start weekly nab-paclitaxel at the next dose level, 10 mg/kg, while the previous cohort is still receiving AC chemotherapy (with MEDI4736 at 3 mg/kg). If 1 patient experiences DLT during either the nab-paclitaxel or AC parts of the therapy, 3 additional patients will be enrolled at the 3 mg/kg dose-level in combination with the chemotherapy part of interest. If none of these 3 additional patients experience DLT (i.e. the final observed DLT rate is 1 of 6), the dose is escalated to 10 mg/kg for the given chemotherapy part. If 2 or more patients experience DLT among the first 6 patients treated at the 3 mg/kg dose level, the study will be halted and dose de-escalation will be considered as an amendment to the trial after consultation with the sponsor. If 2 or more patients experience DLT among the first 3 patients treated at 3 mg/kg dose level, the study will also be halted and dose de-escalation will be considered as an amendment to the trial.

Using the above design, the probabilities of halting dose escalation, in each treatment part, for true rates of DLT ranging from 5% to 70% are as follows:

True rate of DLT:	5%	10%	20%	30%	40%	50%	60%	70%
Probability of halting dose escalation:	0.03	0.09	0.29	0.51	0.69	0.83	0.92	0.97

10 mg/kg MEDI4736 dose level

If dose escalation is feasible, the next cohort of patients will receive MEDI4736 at 10 mg/kg dose concomitant with chemotherapy. Accrual will be halted after the first 3 patients are enrolled at the 10 mg/kg dose until DLT assessment is complete for nab-paclitaxel (i.e. all 3 patients have completed 12 weeks of nab-paclitaxel chemotherapy). If only 1 patients experiences DLT after the first 3 patients are treated at this dose level, the study will proceed to enroll 3 additional patients at the 10 mg/kg dose level in combination with nab-paclitaxel. If none or only 1 of these additional 3 patients show DLT (final observed DLT 1 of 6), this dose level will be moved forward to the Phase II portion for efficacy assessment and accrual will start on the nab-paclitaxel part of treatment while patients are completing the AC part of their therapy. If 2 or more patients experience DLT among the first 6 patients treated at the 10 mg/kg dose level, the dose will be de-escalated to 3 mg/kg and this dose is designated as the RP2D for the subsequent Phase II portion of the trial. If 2 or more patients out of the first 3 experience DLT, the dose will be de-escalated to 3 mg/kg dose and this dose will be moved forward to the Phase II portion for efficacy assessment. DLT will be assessed similarly and the same expansion rules will be followed during the AC part of the treatment.

11.2.2 Efficacy Analyses

The first efficacy will be performed after the first 22 two patients who are enrolled at the RP2D level have received at least 12 weeks (i.e. 6 courses) of MEDI4736, undergone surgery and are evaluated for pCR. Patients who received lower than the RP2D dose during the Phase I part of the study or did not receive a minimum of 6 courses (i.e. 12 weeks) of MEDI4736 will not be included in the interim primary efficacy analysis

Efficacy analysis: The trial will terminate for lack of efficacy if ≤ 7 out of the first 22 evaluable patients experience pCR (Alpha = beta = 10%, probability of early termination if the response rate is 30%=0.67). If > 7 patients experience pCR, accrual will continue until a maximum of 50 evaluable patients are accrued.

If the study proceeds to full accrual after the first interim safety and efficacy analysis, the final efficacy analysis will be as follows:

If ≥ 20 patients who are evaluable for efficacy have pCR (i.e. at least 40% observed pCR rate) then the treatment will considered successful and recommended for further study in a randomized trial. With 50 patients included in the efficacy phase of the study, for the targeted pCR rate of 50% the corresponding 95% confidence interval ranges from 38% to 69%.

A secondary, intent to treat efficacy analysis including all patients who received at least one dose of MEDI4736 at RP2D will also be performed and results will be presented as point estimate of pCR rate with 95% confidence intervals.

11.2.3 Exploratory Analyses

Multivariate associations of immune markers as continuous variables and pCR as dichotomous variable will be evaluated with logistic regression using backward feature elimination (LR test <0.05). Clinical tumor size, clinical nodal status and age will also be included in the model.

RNA expression profiling will also be performed on all base line core needle biopsy samples using RNA sequencing to assess associations between pCR and published immune gene signatures that represent the average expression of sets of highly co-expressed genes that correspond to distinct immune cell types and immune functions. Multivariate associations of the immune signatures as continuous variables and pCR as dichotomous variable will be evaluated with logistic regression using backward feature elimination (LR test <0.05). Clinical tumor size, clinical nodal status and age will also be included in the model.

Whole exome DNA sequencing will also performed to identify somatic mutations and other alterations that could be potential novel predictive markers of response. These will represent exploratory analysis. We will use the Fisher Exact test, which evaluates the significance for over-representation of a specific genomic alteration in the pCR versus no-pCR groups including functional variants in immune genes, overall mutation and neo-antigen load. Due to the sparsely of data at individual variant level, when testing for associations we will aggregate high functional impact variants at gene level and also at pathway level.

Selected immune parameters will also be assessed in residual cancer specimens in cases with less than pCR to assess changes in the immune microenvironment in response to therapy using pair-wise t-test and Bonferroni adjustment of p-values for multiple testing. Correlation coefficients will also be calculated for immune parameters between baseline and residual disease samples.

11.2.4 Interim analyses

One interim efficacy and safety analyses will be performed during the Phase II portion of the study following Simon's two stage clinical trial design as described in sections 11.2.1 and 11.2.2.

11.3 Determination of sample size

The sample size is dictated by the 3+3 and Simons two stage design as described in sections 11.2.1 and 11.2.2.

During the Phase I portion of the trial a minimum of 6 and a maximum of 12 patients will be enrolled.

During the Phase II portion of the trial, we allow replacement of patients for efficacy and safety analysis who are lost for follow up or withdraw from the study for any reasons other than toxicity or disease progression. We also assume that a few accrued patients will not be eligible for the primary efficacy analysis due to receiving fewer than 6 courses of MEDI4736 due to toxicity (all such patients will be included in the safety analyses and secondary efficacy analysis). To allow for replacement and to accrue the required number of eligible patients for primary efficacy analysis, we increase the sample size by 10% to a total sample size 24 (with early stopping for lack of efficacy) or 55 patients (with full accrual) to be included in the Phase II portion of the study.

The combined sample size including both the Phase I and Phase II portions of the trial can range from a minimum of 24 (6 in Phase I plus 18 in Phase II) to a maximum 61 patients (6 in Phase I and 55 in Phase II).

African American extension cohort

We will perform one additional efficacy analysis which includes assessing pCR rates in African America (AA) and non-AA patients separately in the Phase II portion of the trial. In order to make this exploratory analysis, we need at least N=20 AA patients accrued to the study. An AA only extension cohort will remain open until N=20 AA patients are accrued, this may extend the maximum sample size to a total of 71 (as of October 8, 2018; 10 AA patients have been accrued and the total accrual number is 50). Assuming that the baseline pCR=35% for AA patients with TNBC, a cohort of 20 AA patients will have a 76% power to detect an improvement in pCR from 35% to 65% based on the exact binomial test. This is a similar magnitude of improvement, a near doubling of pCR rate, as was observed when trastuzumab was added to paclitaxel/AC

neoadjuvant chemotherapy in HER2 positive breast cancers. The comparison of pCR rates between the two racial cohorts will be performed as exploratory analysis.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

12.2 Ethics and regulatory review

This study will be subject to a two-step peer review following the policies of Yale Comprehensive Cancer Center.

The first step is scientific review by the Protocol Review Committee (PRC) which meets weekly. Further information on the function and membership of the PRC can be found at: http://medicine.yale.edu/cancer/research/trials/services/review.aspx .

The second step is review by the Human Investigations Committee (HIC) which is the Yale equivalent of an institutional review board. All cancer trials are reviewed by a special oncology HIC that meets bimonthly. Further information on human subject protection at Yale and the role of the HIC can be found at: http://www.yale.edu/hrpp/.

12.3 Informed consent

All patients must be counseled about the risk and benefits of the trial and alternative treatment options and signed informed consent before entering the trial. The principal investigator, co-investigators and designated, trained clinical staff and research personnel may obtain the informed consent.

12.4 Changes to the protocol and informed consent form

All changes to the protocol or informed consent will have to be reviewed and approved by the sponsor and the institutional review board before implementation.