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

Protocol

Date: 2/26/2021

Investigational Drug Substance(s)	MEDI4736
Study Number	ESR-14-10265 / Yale HIC 1409014537
Version Number	15
Date	05-Jun-2020

Single arm neoadjuvant Phase I/II study of MEDI4736 (anti-PD-L1 antibody) concomitant with weekly nab-paclitaxel and dose dense doxorubicin/cyclophosphamide (AC) chemotherapy for clinical stage I-III triple negative breast cancer

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Protocol	Date	IRB	IRB Approval
Version 4	25-Mar-15	Initial Submission	N/A – Pre-IRB Approval
Version 5	8-Jul-15	Initial IRB Approval	18-Aug-15
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Version 7	17-Sep-15	Amended in response to FDA clinical deficiencies	N/A – Changes were included in version 8 & submitted to IRB
Version 8	17-Sep-15	Protocol Amendment - FDA Revisions	4-Nov-15
Version 9	12-Feb-16	Protocol Amendment - Updated IB's 8 & 9	6-Apr-16
Version 10	6-Jun-16	Protocol Amendment - Revised Treatment Plan	22-Jul-16
Version 11	24-Jun-16	Protocol Amendment - Accrual earlier cohort	22-Jul-16
Version 12	19-Aug-16	Protocol Amendment - Updated Toxicity Management	7-Dec-16
Version 13	16-Jan-2018	Protocol Amendment – Updated IB & Toxicity Management	25-Apr-2018
Version 14	06-Oct-2018	African American Extension Cohort	26-Mar-2019
Version 15	05-Jun-2020	Updated Toxicity Management	

PROTOCOL SYNOPSIS

Clinical Protocol ESR-14-10265

Study Title: Single arm neoadjuvant Phase I/II study of MEDI4736 (anti-PD-L1 antibody) concomitant with weekly nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide (ddAC) chemotherapy for clinical stage I-III triple negative breast cancer
Protocol Number: ESR-14-10265 **Yale HIC # 1409014537**
Clinical Phase: Single arm, Phase I-II
Study Duration: Accrual is estimated to take 24 to 38 months (2-3 patients/month)
Investigational Product(s) and Reference Therapy:

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The investigational product is MEDI4736 which will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.

Routine, standard of care chemotherapy will be given together with the investigational product and will include weekly nab-paclitaxel x12 treatments followed by every two-week doxorubicin, cyclophosphamide (ddAC) x 4 treatments.

Research Hypothesis: Our hypotheses are: (i) Anti-PD-L1 therapy with MEDI4736 administered concomitantly with weekly nab-paclitaxel followed by MEDI4736 concomitant with ddAC neoadjuvant chemotherapy will induce higher pathologic complete response (pCR) rate (≥55%) in triple negative breast cancer than historical pCR rates (30-40%) observed with chemotherapy alone. (ii) We also hypothesize that MEDI4736 can be safely co-administered at full dose with sequential with nab-paclitaxel (100mg/m2) and ddAC (60 mg/m^2 and 600 mg/m^2 respectively)

Objectives:

Primary Objectives:

The primary objective of the Phase I portion of the trial is to assess the safety of MEDI4736 combined with chemotherapy and determine if full dose of MEDI4736 can be administered concomitantly with full dose weekly nab-paclitaxel followed by dose-dense AC chemotherapies, respectively.

The primary objective of the Phase II portion of the study is to estimate the pCR rate with MEDI4736 in combination with weekly nab-paclitaxel x 12 treatments followed by MEDI4736 in combination with ddAC x 4 treatments for estrogen receptor (ER), progesterone receptor (PR) and HER2 negative (triple negative, TNBC), clinical stage I-III breast cancer. Pathologic complete response is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e. ypT0/Tis ypN0).

Secondary Objectives:

To assess the safety and toxicity of adding anti-PD-L1 antibody, MEDI4736 to standard of care neoadjuvant chemotherapy in the Phase II portion of the trial. Safety will be assessed by using Common Terminology Criteria for Adverse Events, Version 4.3. We will also monitor for events of special clinical interest with a suspected auto-immunologic etiology including grade ≥3 colitis, hyperthyroidism, hypophysitis, hypothyroidism, pneumonitis, rash and anti-drug-antibody (ADA) immune complex disease (manifested by symptoms of arthralgias, abdominal pain, back pain, and vasculitis). For patients included in the Phase II portion of the trial, toxicity will be reported separately for acute toxicities observed on-therapy and for delayed toxicities observed during a 90-day follow up period after completion of therapy. Acute toxicities will also be reported separately for the combination with nab-paclitaxel and dose dense AC parts of the treatment.

To assess the safety and toxicity of adding anti-PD-L1 antibody, MEDI4736 to standard of care neoadjuvant chemotherapy in the Phase II portion of the trial. Safety will be assessed by using Common Terminology Criteria for Adverse Events, Version 4.3. We will also monitor for events of special clinical interest with a suspected auto-immunologic etiology including grade ≥3 colitis, hyperthyroidism, hypophysitis, hypothyroidism, pneumonitis, rash and anti-drug-antibody (ADA) immune complex disease (manifested by symptoms of arthralgias, abdominal pain, back pain, and vasculitis). For patients included in the Phase II portion of the trial, toxicity will be reported separately for acute toxicities observed on-therapy and for delayed toxicities observed during a 90-day follow up period after completion of therapy. Acute toxicities will also be reported separately for the combination with nab-paclitaxel and dose dense AC parts of the treatment.

Exploratory Objectives:

To assess correlation between response to therapy and immune parameters of the tumor at baseline and post-treatment in patients who have residual cancer after therapy. Tissues and blood will also be stored for future studies.

Study Design:

The study will have an initial lead in safety portion that follows a 3+3 Phase I trial design. The subsequent efficacy assessment portion will follow a Simon's two stage Phase II trial design.

Number of Centers: single center (with option to extend if independent funding from Celgene, Inc becomes available to support the conduct and monitoring of a multicenter trial through CRITERIUM CRO.)

Number of Subjects: Minimum 24 and maximum of 71 patients.

Study Population:

Stage I-III, triple negative breast cancer defined as ER and PR<1% positive and HER2 negative (by FISH or IHC 1+ or 2+) for whom systemic chemotherapy is indicated.

Inclusion Criteria:

1. Newly diagnosed histologically confirmed stage I-III, ER, PR and HER2 negative invasive breast cancer as defined by the ASCO CAP guidelines for whom systemic chemotherapy would be indicated based on physician judgment following standard NCCN practice guidelines.

2. Willing and able to provide written informed consent for voluntary participation in the trial.

3. Willing to undergo a baseline tumor core needle biopsy and blood draws for correlative science studies.

4. Eighteen years of age or older on the day of signing informed consent.

5. Female subjects must either be of non-reproductive potential or must have a negative urine or serum pregnancy test upon study entry.

6. Patients should have adequate organ function to tolerate chemotherapy, as defined by:

- peripheral granulocyte count of > 1,500/mm^3
- platelet count > 100,000/mm^3
- hemoglobin >9 g/dL
- total bilirubin < 1.5 x upper limit of normal (ULN)
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) each < 1.5 x ULN
- serum creatinine < 1.5 x ULN or serum creatinine clearance > 50mL/min
- INR/PT/PTT each < 1.5 x ULN
- TSH within normal limits

Exclusion Criteria:

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients who underwent partial excisional biopsy or lumpectomy, segmental mastectomy or modified radical mastectomy or sentinel node.

2. Patients for whom anthracycline, paclitaxel or antibody therapies are contraindicated

3. Patients with active autoimmune disease or documented autoimmune disease within 2 years. Patients with hypothyroidism that is clinically stable and have normal TSH levels with hormone replacement, or patients with vitiligo or psoriasis not requiring treatment remain eligible for the study.

4. Active or prior documented inflammatory bowel disease (Crohn's disease, ulcerative colitis)

5. Patients with known active hepatitis B or C or HIV infection or with history of tuberculosis.

6. Patients with a syndrome that requires administration of chronic systemic steroids or immunosuppressive agents. Patients who only require intermittent use of bronchodilators or local steroid injections are eligible.

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7. Attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, BCG, and typhoid vaccine.

8. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing effective methods of birth control for at least 6 months after completion of the last dose of MEDI4736 and AC chemotherapy.

9. Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736.

10. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction.

11. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

12. History of primary immunodeficiency.

13. History of allogeneic organ transplant.

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent

15. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

Investigational Product(s), Dose and Mode of Administration:

MEDI4736, either 3 mg/kg or 10 mg/kg, IV infusion every 2 weeks over the entire study treatment period (20 weeks).

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Study Assessments and Criteria for Evaluation:

Safety Assessments:

Toxicities will be assessed every two weeks before each administration of MEDI4736 by complete physical examination and complete review of systems as well as laboratory assessment. Grading of toxicities will be according to the NCI CTCAE v5.0.

During the Phase I portion of the study dose limiting toxicities (DLT) will be considered during the entire 20 weeks of therapy for determination of the Maximum Tolerated Dose/Recommended Phase 2 Dose. The last safety assessment will be 90 days after completion of neoadjuvant therapy. For definitions of DLT see section 6.4

Efficacy Assessments:

The primary efficacy endpoint of pCR will be assessed in the surgically resected cancer and lymph nodes after completion of all chemotherapy by the local pathologist as part of routine care. Pathologic complete response is defined as no invasive cancer in the resected breast tissue and lymph nodes (ypT0/Tis, ypN0). This information will be extracted from the pathology report and patients will be assigned to one of two response categories, pCR or residual disease (RD) for the purpose of primary efficacy analysis.

Pharmacodynamic / Pharmacokinetic Assessments (if applicable):

PK studies will not be performed.

Statistical Methods and Data Analysis:

The Phase I portion of the trial will follow the 3+3 design.
The Phase II portion will follow Simon's two-stage design.

Efficacy Analysis

All patients who received at least 12 weeks of therapy (i.e. 6 courses) with MEDI4736 at the recommended Phase II dose will be included in the primary efficacy analysis. A secondary, intent to treat, efficacy analysis will also be performed and will include all patients who received at last one dose of MEDI4736 at the recommended Phase II dose.

Safety Analysis and Toxicity Reporting

All patients who received at least one dose of MEDI4736 will be included in toxicity analysis. Toxicities will be graded according to NCI CTCAE v5.0.

During the Phase I portion of the study dose limiting toxicities (DLT) will be considered during the entire 20 weeks of therapy for determination of the Maximum Tolerated Dose/Recommended Phase 2 Dose (MTD/RP2D). Definition of DLT/RP2D

During the Phase II portion of the trial, cumulative toxicity results over the entire duration of therapy will be reported. Toxicity will also be reported separately for acute (on-treatment) and delayed (within 90 days after completion of treatment) toxicities and acute toxicities will be reported separately for the combination of MEDI4736 with nab-paclitaxel and the combination of MEDI4736 with dose-dense AC.

Toxicities will be reported as frequency statistics with 95% confidence intervals.

Statistical Plan of Exploratory Biomarker Analysis

The following immune parameters, in order of priority in case of limited tissue availability, will be assessed using quantitative immunohistochemistry in base line core needle biopsies: PD1 (programmed death receptor 1) and PD-L1 and -L2 (programmed death receptor ligands 1 and 2), CD3+, CD4+, CD8+, CD137, FOXP3, OX40, CTLA4 and GITR. Tumor infiltrating lymphocyte (TIL) count will be estimated from an H&E section and quantified as the percent of stromal cells that are lymphocytes. Multivariate associations of these 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 to assess associations between pCR and published immune gene signatures. The 6 immune gene signatures are metagenes corresponding to the average expression of sets of highly co-expressed genes. These metagenes represent semi-quantitative estimates of distinct cell types including plasma cells (IGG metagene), T-cells (CD8A metagene) and antigen-presenting cells (MHC2 metagene) and also capture important immune regulatory pathways such as MHC1 gene expression (MHC1 metagene), STAT1 co-expressed genes (STAT1 metagene) and interferon-inducible genes (IF-I metagene including IFNg) and chemokine signaling through CXCL9 and CXCL1. These metagenes were selected because they have been repeatedly observed in gene expression data, can be assessed reliably and carry prognostic value. Multivariate associations of these immune metagenes 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 be performed to identify somatic mutations and other alterations that could be potential novel predictive markers of response. These will represent exploratory analysis. Sequencing will be performed at the Yale Center for Genome analysis with average depths of $\geq$ 150x. 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, to assess potential association between functional variants in immune genes and response. Due to the sparsely of data at individual variant level, 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.

Sample Size Determination: Total sample size is a minimum of 24 and maximum of 71 patients including both Phase I and phase II portions and allowing for replacement of non-evaluable patients for efficacy at a 10 % loss rate.

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.

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.

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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 patient 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.

Two-stage Phase II portion of the trial

The interim efficacy and toxicity analyses will be performed after the first 22 patients evaluable for primary efficacy analysis. Patients will be considered evaluable for efficacy assessment if they received at least 12 weeks of MEDI4736 at the Recommended Phase 2 dose concomitant with chemotherapy. Patients who received lower than the Recommended Phase 2 dose during the Phase I portion of the trial will not be included in the efficacy analysis. Patients who did not receive at least 12 weeks (i.e. 6 courses) of MEDI4736 are also not eligible for efficacy analysis but will be included in the toxicity assessment. Trial accrual will continue while efficacy and toxicity data is accumulating for the 22 patients.

The trial will terminate for lack of efficacy if < 7 patients out of the first 22 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 patients are accrued.

Safety analysis: 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 (i.e. >7/22 patients have pCR), the trial may reopen after the MEDI4736 dose and schedule is amended to improve safety. With

22 patients in the first stage, there is ≥ 90% chance of observing at least 1 DLT event, if the true underlying rate of the adverse event is ≥ 10%.

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

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

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.

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SCHEDULE OF STUDY ASSESSMENTS

Screening, Treatment Period and Post-treatment follow-up

Assessments to be performed at the times stipulated in the table and as clinically required in the management of a patient.	Screening	Treatment Period (Assessments to be performed pre-infusion unless stated otherwise)				
		Baseline	**Every week**	**Every 2 weeks**	**Every 4 weeks**	**Follow-up after completion of all neoadjuvant therapy**
Day	**-42 to -1**	**Day 1**	**Day 1 of the week**			
Week	**-6 to 1**	**1**	**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12**	**1, 3, 5, 7, 9, 11, 13, 15, 17, 19**	**5, 9, 13, 17**	**22, 26, 33**
Written informed consent/assignment of subject identification number	X					
Preliminary eligibility assessment (investigator's opinion)	X					
Demographic information	X					
Tumour biopsy and blood draw for research	X*					Research blood draw is repeated after week 20 but before surgery
Formal verification of eligibility criteria	X					

Screening, Treatment Period and Post-treatment follow-up

Assessments to be performed at the times stipulated in the table and as clinically required in the management of a patient.	Screening	Treatment Period (Assessments to be performed pre-infusion unless stated otherwise)				
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Medical and surgical history, review of systems		X				X
Hepatitis B and C; HIV if clinically indicated	X					
Urine hCG or serum βhCG[a]	X					
MEDI4736 administration		X		X[c,d]		
Nab-paclitaxel administration		X	X			
ddAC administration				Weeks 13,15,17,19 only		
Physical examination		X		X		X

Screening, Treatment Period and Post-treatment follow-up

Assessments to be performed at the times stipulated in the table and as clinically required in the management of a patient.	**Screening**	**Treatment Period (Assessments to be performed pre-infusion unless stated otherwise)**				
		Baseline	**Every week**	**Every 2 weeks**	**Every 4 weeks**	**Follow-up after completion of all neoadjuvant therapy**
Day	**-42 to -1**	**Day 1**	**Day 1 of the week**			
Week	**-6 to 1**	**1**	**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12**	**1, 3, 5, 7, 9, 11, 13, 15, 17, 19**	**5, 9, 13, 17**	**22, 26, 33**
Vital signs (pre- during and post-infusion vital signs assessments)[b]		X	X	X		X
Weight		X	X	X		X
Electrocardiogram	X		Week 6	Week 17		
Adverse event/serious adverse event assessment		X	Weeks 3, 5, 7,8, 9 and 11	X		X
Concomitant medications		X	Weeks 3, 5, 7,8, 9 and 11	X		X
ECOG performance status		X	Weeks 3, 5, 7,8, 9 and 11	X		
Serum AST, ALT, T Bili	X[c,e]				X	X
TSH (free T3 and T4 if TSH is elevated)	X[c,e]				X	

Screening, Treatment Period and Post-treatment follow-up

Assessments to be performed at the times stipulated in the table and as clinically required in the management of a patient.	Screening	Treatment Period (Assessments to be performed pre-infusion unless stated otherwise)				
		Baseline	**Every week**	**Every 2 weeks**	**Every 4 weeks**	**Follow-up after completion of all neoadjuvant therapy**
Day	**-42 to -1**	**Day 1**	**Day 1 of the week**			
Week	**-6 to 1**	**1**	**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12**	**1, 3, 5, 7, 9, 11, 13, 15, 17, 19**	**5, 9, 13, 17**	**22, 26, 33**
CBC/Diff	X[a,e]		X	X		X
PT, PTT, INR	X[a,e]					
Urinalysis	X[a,e]				X	

[a] Pre-menopausal female subjects of childbearing potential only
[b] Subjects will have their temperature, blood pressure, pulse, and respiratory rate measured before, during and after the infusion as per hospital standard operating procedure.
[c] MEDI4736 will be administered on the same day as nab-paclitaxel in weeks 1-12. Nab-paclitaxel will be administered first.
[d] dose dense doxorubicin plus cyclophosphamide will be administered on day 1 of Weeks 13, 15, 17, and 19. MEDI4736 will be administered on day 2 of weeks 13, 15, 17, and 19, approximately 24 hours after the administration of doxorubicin + cyclophosphamide immediately after subcutaneous administration of pegfilgrastrim, as outlined in Section 5.3.2.
[e] Laboratory test results that are considered abnormal, but continue to meet the eligibility requirements, during the screening phase will be repeated at baseline (C1D1).

*Research tissue and blood can be drawn any time after consenting and before receiving the first treatment; this includes Day 1 before administration of therapy.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
C_max	peak concentration
C_max,ss	peak concentration at steady state
C_min	trough concentration
C_min,ss	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
ddAC	Dose dense doxorubicin and cyclophosphamide chemotherapy
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

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Abbreviation or special term	Explanation
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry
IL	interleukin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody

Abbreviation or special term	Explanation
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks

Abbreviation or special term	**Explanation**
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t_½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
T_max	time to peak concentration
T_max,ss	time to peak concentration at steady state
TNBC	Triple Negative Breast Cancer
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

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1. INTRODUCTION

1.1 Background

Triple negative breast cancer

Each year approximately 40-45,000 women are diagnosed with clinical stage I-III TNBC which has the least favorable prognosis among the different breast cancer subtypes. The only systemic treatment option for patients with early stage TNBC to improve their chance of survival is chemotherapy. The last new chemotherapy agent approved by the US FDA as adjuvant therapy to improve survival of this disease was paclitaxel close to 20 years ago. While TNBC includes some of the most chemotherapy sensitive tumors, pCR rates do not exceed 35-40 % with the most widely used third generation neoadjuvant chemotherapy regimens that include a taxane (with or without a platinum agent) and anthracycline (Rouzier et al, 2005). Pathologic complete response is associated with excellent long term disease free and overall survival in this disease subset (Liedtke et al, 2008). On the other hand, patients with TNBC and residual cancer after neoadjuvant therapy have poor prognosis with 3-year recurrence rates around 50% (Symmans et al, 2007). The US FDA has recently recognized this strong association between pCR and long term survival in TNBC and HER2 positive breast cancers and expressed interest in accepting this endpoint for accelerated drug approval in these cancers (FDA guidance, 2012). In September 2013, Pertuzumab (Perjeta™) was approved for HER2 positive breast cancer in combination with trastuzumab and docetaxel as neoadjuvant therapy on the basis of increased pCR rates (US FDA, 2013). The goal of this research is to estimate if inclusion of an immune checkpoint inhibitor could increase pCR rate above historical rates.

1.2 MEDI-4736 Background

Investigators should be familiar with the current MEDI4736 Investigator Brochure (IB). MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.2.1 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the MEDI4736 Investigator's Brochure (IB).

In general, treatment with MEDI4736 was not associated with any serious drug-related adverse effects in cynomolgus monkeys. Adverse findings in a non-GLP (good laboratory practice) pharmacokinetic/pharmacodynamic (PK/PD) and dose range-finding study, and in a separate GLP compliant 4-week repeat-dose toxicity study were both consistent with antidrug antibody (ADA)-associated morbidity and mortality in cynomolgus monkeys. The death of a single animal in the PK/PD and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the microscopic pathology, in a single animal in the 4-week repeat-dose study indicated ADA-mediated pathologic effects including immune complexes in tissues identified by immunohistochemistry. The NOAEL (No Observed Adverse Effect Level) of MEDI4736, the highest dose level at which chronic exposure to the substance shows no adverse effects, was 100 mg/kg that corresponds to the highest dose tested in preclinical toxicity studies.

The IB may be updated during the conduct of this trial; each update will be reviewed and submitted to the HIC. Any new drug-related human toxicity information, or preclinical toxicity that is relevant for humans, will be incorporated into the informed consent form.

1.2.2 Summary of clinical experience

Clinical experience with MEDI4736 is fully described in the current version of the MEDI4736 Investigator's Brochure (IB).

As of the data cutoff date of 14 Jul 2014, a total of 509 subjects have been enrolled and treated with MEDI4736 in 10 ongoing clinical studies: 5 employing MEDI4736 as monotherapy and 5 as combination therapy. No studies have yet been completed.

The IB may be updated during the conduct of this trial; each update will be reviewed and submitted to the HIC. Any new drug-related human toxicity information, or preclinical toxicity that is relevant for humans, will be incorporated into the informed consent form.

Pharmacokinetics and Product Metabolism

MEDI4736 monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-

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proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥ 3 mg/kg, suggesting that the nonlinear PK of MEDI4736 is likely due to saturable target-mediated clearance. Exposures following multiple doses (currently up to a maximum of 26 doses) demonstrated accumulation consistent with PK parameters estimated from the first dose.

Suppression of free soluble PD-L1 (sPD-L1) was correlated with MEDI4736 PK concentrations. Following administration of MEDI4736 monotherapy, free sPD-L1 levels were below the lower limit of quantitation (LLOQ) in the majority of subjects with available data (n = 38) at all time points following IV doses ≥ 1 mg/kg every 2 weeks (Q2W).

Overall, a low incidence of ADA was observed. Of the 220 subjects who received MEDI4736 monotherapy and for whom PK/ADA data were available, 5 were detected ADA positive, with an impact on PK/pharmacodynamics reported in 1 subject.

Safety

As of 14Jul2014, no identified risks are clearly associated with the use of MEDI4736. Important potential risks based on the mechanism of action of MEDI4736 and its related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy. Additional important potential risks include infusion-related reactions, hypersensitivity, serious allergic reactions, serious infections, and immune complex disease.

The majority of the safety data are from the monotherapy study, CD-ON-MEDI4736-1108, specifically the 10 mg/kg Q2W cohort (N = 393). In this cohort, the most frequently reported (≥ 10% of subjects) adverse events (AEs; all grades, regardless of causality) were fatigue (29.8%), nausea (20.1%), dyspnea (19.6%), decreased appetite (19.1%), constipation (14.0%), diarrhea and vomiting (12.5% each), cough (11.5%), pyrexia and back pain (10.4% each), and rash (10.2%). In approximately half of the subjects, the highest AE severity was Grade 1 (25.2% of subjects) or Grade 2 (22.9% of subjects). Most of these events were managed clinically without the need for dose modifications or delays. Grade 3 or higher AEs that occurred in > 1% of subjects were dyspnea (5.1%), increased gamma-glutamyltransferase (3.3%), fatigue, general physical health deterioration, increased aspartate aminotransferase, and back pain (2.3% each), anemia and dehydration (1.8% each), and abdominal pain, vomiting, sepsis, syncope, and hypotension (1.3% each). Treatment-related Grade 3 AEs in 2

or more subjects were fatigue (4 subjects), increased gamma-glutamyltransferase (3 subjects), and vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, and arthralgia (2 subjects each). There were 2 subjects with treatment-related Grade 4 events (hypercalcemia, fatigue) and 1 subject with a treatment-related Grade 5 event (angiopathy). In general, Grade 3 or higher AEs were manageable and reversible with standard toxicity management guidelines.

Serious adverse events (SAEs) and other significant AEs occurred in fewer than one-third of subjects treated with MEDI4736 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108. The most frequently reported SAEs (regardless of causality; > 5 subjects) were dyspnea (15 subjects), general physical health deterioration (9 subjects), pyrexia (8 subjects), back pain and abdominal pain (7 subjects each), and dehydration and pleural effusion (6 subjects each). One subject (with Stage IV lung cancer and a history of cardiac disease) died due to angiopathy considered by the investigator as related to MEDI4736. Adverse events that resulted in permanent discontinuation of MEDI4736 in ≥ 2 subjects were dyspnea (7 subjects), general physical health deterioration (5 subjects), and death, increased transaminases, pulmonary embolism, and respiratory failure (2 subjects each).

No dose-limiting toxicities (DLTs) have been reported in any of the dose-escalation cohorts of the monotherapy studies. Overall, the AE profile of MEDI4736 was consistent with the pharmacology of the target. No tumor types appeared to be associated with unique AEs.

Efficacy

As of 14Jul2014, partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00002) and 1 combination therapy study of MEDI4736 plus tremelimumab (D4190C00006). Tumor assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines (Eisenhauer et al, 2009).

Clinical activity has been observed across the 3 studies. In Study CD-ON-MEDI4736-1108, 169 of 414 subjects treated with MEDI4736 (all dose levels) were evaluable for response analysis, which included subjects who had at least 24 weeks of follow-up as of the data cutoff date and had either at least 1 post-baseline tumor assessment or experienced clinical progressive disease (PD) or death. Nineteen subjects (11.2%) had a best overall response of complete response (CR)/partial response (PR; confirmed and unconfirmed). The disease control rate (DCR; CR + PR + stable disease [SD] ≥ 12 weeks) was 32% (54 of 169 subjects).

Tumoral programmed cell death ligand 1 status was known for 143 of the 169 evaluable subjects, of whom 30 had tumors that were PD-L1 positive. A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) PD-L1-positive subjects and in 6 of 113 (5.3%) PD-L1-negative subjects. By tumor type, responses were observed in subjects with non-small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), hepatocellular carcinoma (HCC), cutaneous melanoma, gastroesophageal cancer, and pancreatic adenocarcinoma. In Study D4190C00002, 12 of 18 subjects had at least 1 post-baseline tumor assessment. One subject had a best overall response of PR (unconfirmed) and 6 subjects had SD (irrespective of tumoral PD-L1 expression). In Study D4190C00006, 13 of 18 subjects had at least 1 tumor assessment. Five subjects had best overall responses of PR (1 confirmed and 4 unconfirmed) and 3 subjects had SD (again irrespective of tumoral PD-L1 expression).

Drug Interactions

There are no known clinically significant interactions of MEDI4736 with other medicinal products, but no formal drug-drug interaction studies have been conducted with MEDI4736.

Pregnancy and Lactation

Nonclinical assessment of the potential reproductive and developmental toxicity of MEDI4736 has not been conducted. It is not known whether MEDI4736 is excreted in breast milk.

1.3 Research hypothesis

Our hypotheses are that MEDI4736 administered concomitantly with weekly nab-paclitaxel and dose-dense AC (ddAC) neoadjuvant chemotherapy will induce higher pathologic complete response (pCR) rate (≥55%) in triple negative breast cancer than historical pCR rates (30-40%) observed with the same chemotherapy regimen chemotherapy alone. We also hypothesize that MEDI4736 can be administered safely at full dose concomitant with nab-paclitaxel (100mg/m2) and ddAC (60 mg/m^2 and 600 mg/m^2 respectively)

1.4 Rationale for conducting this study

There are few molecular prognostic markers for survival and predictive markers for chemotherapy sensitivity for Stage I-III TNBC. High level of lymphocytic infiltration in the primary tumor (TIL) is the only consistent prognostic marker for better survival in the absence of any systemic therapy and it also serves as a predictive marker for higher pCR to neoadjuvant chemotherapy in these cancers (Bianchini et al, 2010; Loi et al, 2013; Denkert et

al, 2010). These observations raise the possibility that antitumor immune response may contribute to the better clinical outcome. Multiple different preclinical studies indicate that immune cells in the tumor microenvironment, particularly activated cytotoxic T cells, partially mediate chemotherapy response (Bracci et al, 2014, Zitvogel et al, 2008). The CD80/CTLA4 and PD1/PD-L1/L2 receptor-ligand interactions play a major role in suppressing cytotoxic T cell activity. In the lymph nodes, PD-L1 expressed on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and inhibits their activity (Keir et al, 2008; Park et al, 2010). In the tumor microenvironment, PD-L1 is also expressed on tumor cells and can suppress anti-tumor immunity (Zou et al, 2008). Several studies using different immunohistochemistry methods and in situ mRNA measurements have demonstrated that PD-L1 is expressed by breast cancer cell lines and also by 20-60% of TNBC (Schalper et al, 2014; Soliman et al, 2014; Mittendorf et al, 2014; Ghebeh et al, 2008). The relationship between PD-L1 expression and response to MEDI4736 is currently unclear, objective tumor response in lung cancer and melanoma appear to be more common in PD-L1 positive cancers (defined as > 1% IHC positivity) but is also seen in PD-L1 negative cases (Antonio et al, ESMO 2014 abstract 7629). Currently, there is no agreed upon standard clinical test to determine PD-L1 expression, and different research groups and companies often use different methods. For these reasons, this study will not restrict eligibility based on PD-L1 expression.

In the past few years new drugs emerged that can boost local anti-tumor immune response by inhibiting the PD1 mediated immune checkpoints. Antibodies that target the interaction between PD1 and its ligands can enhance the cytotoxic activity of antitumor T cells by removing the inhibitory signal (Blank et al, 2006). Multiple different drugs that block the PD1 ligand interaction has been shown to induce objective and lasting tumor responses in multiple different tumor types including lung cancer, melanoma, head and neck cancer and bladder cancer (Brahmer et al, 2012; Hamid et al, 2013; Herbst et al, 2013; Kirskwood et al, 2010). PD1-targeted drugs as single agent therapy in Phase I trials also showed objective responses in 15-20% of metastatic TNBC (San Antonio Breast Cancer Symposium, 2014, Abs #S1-09) .

1.5 Benefit/risk and ethical assessment

All patients who participate in this trial will receive the currently most effective sequential taxane and anthracycline combination neoadjuvant chemotherapy, which is considered standard of care in this patient population. Long-term disease-free and overall survival are the same for patients who receive the same chemotherapy, regardless if the treatment is given preoperatively (neoadjuvant treatment) or postopratively (adjuvant therapy). Administration of chemotherapy preoperatively provides an opportunity to directly assess the cytotoxicity of a treatment regime. It also yields personal benefits for patients in the form of tumor shrinkage that allows smaller resection and providing important prognostic information that resides in the pathologic tumor stage. Patients with TNBC and extensive residual cancer after chemotherapy have very poor prognosis which could motivate patients to seek out further adjuvant clinical trials to improve outcome. It is widely held that increasing the pCR rate in

TNBC may increase long-term survival. However, there is considerable controversy about what degree of increase in pCR rate would translate to what level of improvement in survival. The ultimate goal of this trial is to attempt to improve pCR rate beyond what the current best regimens can accomplish, we hope that the magnitude of improvement will be sufficient to increase long-term survival which can be demonstrated in the future, in a much larger randomized trial.

The risk inherent to this clinical study is increased toxicity due to inclusion of MEDI4736 in the treatment. MEDI4736 monotherapy at the 10 mg/kg dose administered every two weeks was well tolerated. No dose limiting toxicities were reached in any of the dose escalation trials. However, the most frequent adverse events, including fatigue, dyspnea, decreased appetite and liver enzyme elevations, are also adverse events that can be caused by the chemotherapy drugs used in this trial. Safety monitoring and dose reduction guidelines are built into the trial to minimize harm.

Currently there are no known clinically significant drug interactions with MEDI4736 and other drugs. Humanized monoclonal antibodies, as a drug class, have also not demonstrated significant interactions with chemotherapy drugs.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of the Phase I portion of the trial is to assess the safety of MEDI4736 combined with chemotherapy and determine if full dose of MEDI4736 can be administered in combination with weekly nab-paclitaxel x 12 treatments followed by MEDI4736 in combination with ddAC x 4 treatments.

The primary objective of the Phase II portion of the study is to estimate the pCR rate, defined as no invasive cancer in the resected breast tissue and lymph nodes (ypT0/Tis, N0), after neoadjuvant (pre-operative) therapy with MEDI4736 in combination with weekly nab-paclitaxel x 12 treatments followed by MEDI4736 in combination with ddAC x 4 treatments for estrogen receptor (ER), progesterone receptor (PR) and HER2 negative (triple negative, TNBC), clinical stage I-III breast cancer.

2.2 Secondary objective(s)

To assess the toxicity of adding anti-PD-L1 antibody, MEDI4736 to neoadjuvant chemotherapy with standard of care nab-paclitaxel and ddAC. Safety will be assessed by adverse experiences using Common Terminology Criteria for Adverse Events, Version 4.0. and will also monitor for

events of special clinical interest with a suspected auto-immunologic etiology including grade ≥3 colitis, hyperthyroidism, hypophysitis, hypothyroidism, pneumonitis, rash and anti-drug-antibody (ADA) immune complex disease (manifested as symptoms of arthralgia, serum-sickness, abdominal pain, back pain, and vasculitis). Acute toxicities will be reported for the entire 20-week duration of therapy for patients included in the Phase II portion of the trial and also separately for the combination with nab-paclitaxel and dose dense AC respectively. Late toxicities will also be collected and reported separately for 90 days after completion of treatment.

2.3 Exploratory objective(s)

Exploratory correlative science objectives include correlation of baseline and post-treatment residual cancer immune parameters of the tumor with pCR.

The following immune parameters, in order of priority in case of limited tissue availability, will be assessed using quantitative immunohistochemistry in base line core needle biopsies: PD1 (programmed death receptor 1) and PD-L1 and -L2 (programmed death receptor ligands 1 and 2), CD3+, CD4+, CD8+, CD137, FOXP3, OX40, CTLA4 and GITR. Tumor infiltrating lymphocyte (TIL) count will be estimated from an H&E section and quantified as the percent of stromal cells that are lymphocytes.

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. The 6 immune gene signatures are metagenes corresponding to the average expression of sets of highly co-expressed genes. These metagenes represent semi-quantitative estimates of distinct cell types including plasma cells (IGG metagene), T-cells (CD8A metagene) and antigen-presenting cells (MHC2 metagene) and also capture important immune regulatory pathways such as MHC1 gene expression (MHC1 metaene), STAT1 co-expressed genes (STAT1 metagene), interferon-inducible genes (IF-I metagene) and chemokine signaling through CXCL9 and CXCL1. These metagenes were selected because they were repeatedly observed in gene expression data, can be assessed reliably and carry prognostic value.

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. Sequencing will be performed at the Yale Center for Genome analysis with average depths of $\geq$ 150x.

Blood will be collected at baseline before starting therapy and after completion of all neoadjuvant treatment for future studies.

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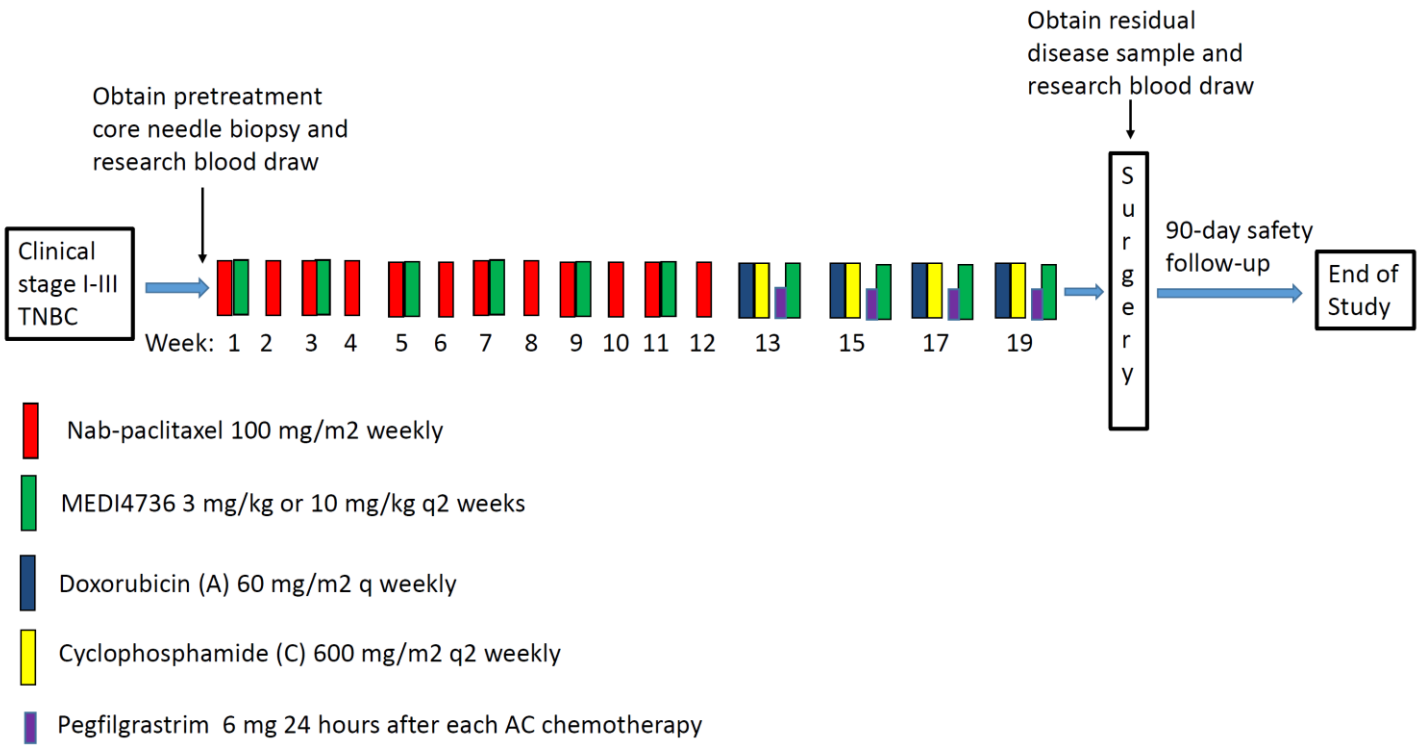
3. STUDY DESIGN

3.1 Overview of study design

The study will have an initial lead in safety portion that follows a 3+3 Phase I trial design with two dose levels of MEDI4736 (3mg/kg and 10mg/kg). The subsequent efficacy assessment portion will follow a Simon's two stage Phase II trial design including patients from the Phase I portion of the trial who have received at least 12 weeks of therapy with the recommended Phase II dose of MEDI4736.

3.2 Study schema

Figure 1 Trial Schema



3.3 Study Oversight for Safety Evaluation

During the Phase I portion of the trial, the first 3 patients will be enrolled at dose level of 3 mg/kg MEDI4736 concomitant with chemotherapy. The DLT evaluation period will extend from Cycle 1 Day 1 through to the end of the 20-week treatment period. Accrual will be halted after the 3rd patient enters the trial and until all 3 patients have had toxicity assessment at the end of the DLT evaluation period (20 weeks). If 1 patient experiences DLT during the entire treatment period (20 weeks), 3 additional patients will be enrolled at the 3 mg/kg dose-level. 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. Also, if 2 or more patients experienced DLT among the first 3 patients treated at 3 mg/kg dose level, the study will be halted and dose de-escalation will be considered as an amendment to the trial.

During the Phase II portion of the trial **t**he following toxicities require permanent discontinuation of MEDI4736: Any grade ≥3 toxicity (non-hematologic or hematologic) that is unexpected or probably casually related to MEDI4736 including infusion reaction. Grade ≥ 3 colitis. Grade ≥ 3 events of potential immunologic etiology including but not limited to nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, Guillain-Barré syndrome, or myasthenia gravis. Grade > 3 endocrinopathy that is symptomatic despite adequate hormone replacement therapy. AST or ALT >5 x ULN. **T**otal serum bilirubin >3 x ULN. Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations.

4. SUBJECT SELECTION

4.1 Inclusion criteria

For inclusion in the study, patients must fulfill all of the following criteria:

1. Newly diagnosed histologically confirmed stage I-III, ER, PR and HER2 negative invasive breast cancer as defined by ASCO CAP guidelines for whom systemic chemotherapy would be indicated based on physician judgment following standard NCCN practice guidelines (Theriault et al, 2013).

2. Patients with prior history of stage I-III breast cancer currently without evidence of metastatic disease are eligible if can tolerate further chemotherapy, patients with newly diagnosed synchronous bilateral breast cancers are also eligible if at least one tumor is triple negative (response will be assessed in both breasts if invasive cancer is present in both).

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3. Willing and able to provide written informed consent for voluntary participation in the trial.

4. Willing to undergo a baseline tumor core needle biopsy for correlative science studies. This study does not restrict eligibility based on PD-L1 expression because the relationship between PD-L1 expression and response is not fully understood and there are no standardized and validated clinical tests to assess PD-L1 expression.

5. Eighteen years of age or older on the day of signing informed consent.

6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative urine or serum pregnancy test upon study entry.

7. Patients should have adequate organ function to tolerate chemotherapy, as defined by:

- peripheral granulocyte count of > 1,500/mm^3
- platelet count > 100,000/mm^3
- hemoglobin >9 g/dL
- total bilirubin < 1.5 x upper limit of normal (ULN)
- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) each < 1.5 x ULN
- serum creatinine < 1.5 x ULN or serum creatinine clearance > 50mL/min
- INR/PT/PTT each < 1.5 x ULN
- TSH within normal limits

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients who underwent partial excisional biopsy or lumpectomy, segmental mastectomy or modified radical mastectomy or sentinel node biopsy are not eligible because they cannot be assessed accurately for pathologic response.

2. Patients for whom anthracycline, paclitaxel or antibody therapies are contraindicated:
- Hypersensitivity reactions to any of the medications or to humanized monoclonal antibodies

- History of congestive heart failure
- Myocardial infarction within the past 12 months
- Pre-existing peripheral neuropathy ≥ grade 2
- Prior anthracycline therapy with ≥ cumulative dose of 240 mg/m2

3. Patients with active autoimmune disease or documented autoimmune disease within 2 years, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

4. Patients with hypothyroidism that is clinically stable and have normal TSH levels with hormone replacement, or patients with vitiligo or psoriasis not requiring treatment remain eligible for the study.

5. Active or prior documented inflammatory bowel disease (Crohn's disease, ulcerative colitis).

6. Patients with known active hepatitis B or C or HIV infection or with history of tuberculosis.

7. Patients with a syndrome that requires administration of chronic systemic steroids or immunosuppressive agents. However, patients that require intermittent use of bronchodilators or local steroid injections are eligible.

8. Attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

9. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing effective methods of birth control for at

least 6 months after completion of the last dose of MEDI4736 and AC chemotherapy. (see section 7.1).

10. Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736.

11. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Bazett's Correction.

12. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

13. History of primary immunodeficiency.

14. History of allogeneic organ transplant.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

16. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

4.3 Withdrawal of Patients from Study Treatment and/or Study

Permanent discontinuation of study treatment

An individual patient will not receive any further investigational product if any of the following occur:

1. Withdrawal of consent for any reason

2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing

3. Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

4. Pregnancy or intent to become pregnant

5. Any patient showing clinical or radiological sign of progression of her disease during therapy. Further treatment will be individualized for these patients by their primary treating physician. Options include more chemotherapy with different agents, surgery or preoperative radiation. For analysis purposes these patients will be considered as residual disease (RD).

6. Any patient developing dose limiting toxicity (as defined in Section 6.5) or unacceptable toxicity (as defined in section 6.6) will discontinue therapy in the study. Further treatment will be individualized for these patients by their primary treating physician. Options include more chemotherapy with different agents, surgery or preoperative radiation.

7. Grade ≥ 3 infusion reaction

8. Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits

9. Initiation of alternative anticancer therapy including another investigational agent

Patients who received at least one dose of MEDI4736 but subsequently were permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1.

Withdrawal of consent

If consent is withdrawn, the patient will not receive any further investigational product or further study observation.

4.4 Replacement of patients

Replacement of patient, lost due to withdrawal of consent or lost for follow up for reasons other than toxicity or progression (e.g. transfer of care to other institutions) is allowed.

5. INVESTIGATIONAL PRODUCT(S)

5.1 MEDI4736

The Investigational Products Supply section of AstraZeneca/MedImmune will supply MEDI4736 to the investigator as a concentrate for solution for infusion.

5.1.1 Formulation/packaging/storage

MEDI4736 is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (w/v) saline for IV infusion.

Unopened vials of liquid MEDI4736 must be stored at 2°C to 8°C (36°F to 46°F). MEDI4736 must be used within the individually assigned expiry date on the label.

In use storage and stability

Total in-use storage time from needle puncture of MEDI4736 vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. MEDI4736 does not contain preservatives and any unused portion must be discarded.

5.1.2 Doses and treatment regimens

MEDI4736 will be administered every 2 weeks at doses of either 3 mg/kg or 10 mg/kg during the phase I portion of this study. The dose of MEDI4736 in the phase II portion will be either 3 mg/kg or 10 mg/kg, as determined in the phase I portion.

There will be no intra-patient dose escalation permitted.

5.1.3 Study drug preparation

Calculate the dose volume of MEDI4736 and number of vials needed for the subject to achieve the accurate dose according to Appendix A.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

An additional volume of 0.9% (w/v) saline equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736.

The calculated volume of MEDI4736 is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

5.1.4 Dose administration

MEDI4736 will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein.

Following preparation of MEDI4736, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.

The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the

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infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.

5.1.5 Monitoring of dose administration

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment (see Section 8.2).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.1.6 Accountability and dispensation

Study drug will be shipped to the Oncology Investigational Drugs Pharmacy and dispensed under the supervision of Thomas M. Ferencz R.Ph., BCOP, Senior Clinical Pharmacy Specialist, Oncology Investigational Drugs, Smilow Cancer Hospital at Yale New Haven Hospital Oncology Pharmacy, 8th floor, room 8-110, 35 Park St., New Haven, CT 06510. Phone (203)-200-4455, Fax (203)-200-4445, email: Thomas.Ferencz@ynhh.org.

5.1.7 Disposition of unused investigational study drug

Unused drugs will be destroyed as per the policy of the Oncology Investigational Drugs pharmacy of Smilow Cancer Hospital.

5.2 Nab-paclitaxel

Nab-paclitaxel (Abraxane®, NDC 68817-134-50) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel is the active anti-tumor agent in the particles that disrupts microtubule dynamics and induce cell death.

5.2.1 Formulation/packaging/storage

Nab-paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Nab-paclitaxel is considered standard of care chemotherapy and will be stored and dispensed following the pharmacy policies of Smilow Cancer Hospital.

5.2.2 Doses and treatment regimens

Nab-paclitaxel 100mg/m IV will be administered together with, but prior to, MEDI4736 following standard chemotherapy administration practice of Smilow cancer hospital. No steroid premedication is required for this drug in routine practice. Patients will receive 12 weekly treatments and subsequently on week 13 will start the ddAC part of their treatment.

5.2.3 Product preparation

Preparation and administration of nab-paclitaxel will follow standard hospital policy for routine chemotherapy.

5.2.4 Dose administration

Nab-paclitaxel 100 mg/m^2. will be administered as a 30 minute IV infusion once every week for 12 treatments (through weeks 1-12) following institutional treatment guidelines.

5.2.5 Monitoring of dose administration

Each patient will be monitored for vital signs and assessed for symptoms by the chemotherapy nurse before, during and after administration of treatment as per institutional guidelines.

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5.2.6 Accountability and dispensation

Accountability and dispensation of nab-paclitaxel will follow oncology pharmacy policy for routine chemotherapy.

5.2.7 Disposition of unused drug

Disposition of nab-paclitaxel will follow oncology pharmacy policy for routine chemotherapy.

5.3 Doxorubicin combined with Cyclophosphamide (AC)

Doxorubicin is an antineoplastic antibiotic. It has multiple mechanisms of action including inhibition of topoisomerase II, generation of free oxygen radicals and induction of apoptosis.

Cyclophosphamide is a synthetic antineoplastic drug chemically related to nitrogen mustard. Cyclophosphamide is metabolized in the liver to active alkylating compounds by the microsomal oxidase system. These metabolites induce DNA cross links which lead to cell death.

Doxorubicin and cyclophosphamide are used in combination due to synergistic anticancer activity and have been shown to improve survival of early stage breast cancer in randomized clinical trials.

5.3.1 Formulation/packaging/storage

Doxorubicin Hydrochloride Injection: Vials contain 10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL, 150 mg/75 mL, and 200 mg/100 mL Doxorubicin hydrochloride as a clear red solution. Lyophilized Doxorubicin Hydrochloride for Injection: Vials contain 10 mg, 20 mg, 50 mg, and 150 mg Doxorubicin hydrochloride as a red-orange lyophilized powder.

Cyclophosphamide is supplied in 500 mg, 1000mg and 2000mg vials (as anhydrous cyclophosphamide).

5.3.2 Doses and treatment regimens

One week after completion of nab-paclitaxel, 4 additional courses of chemotherapy consisting of Doxorubicin 60 mg/m^2 IV and Cyclophosphamide 600 mg/m^2 IV once every 14 days (through weeks 13-20) will be administered. Approximately 24 hours after each AC chemotherapy, pegfilgrastrim 6 mg (Neulasta™) will be administered subcutaneously followed by MEDI4736 intravenously as described in section 5.1.

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5.3.3 Product preparation

Preparation and administration of will follow standard hospital policy for routine chemotherapy.

5.3.4 Dose administration

Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 will be administered following institutional treatment guidelines for routine chemotherapy. The first course of treatment will be administered without decadron pre-medication. If clinically significant nausea or vomiting occurs subsequent courses will be administered with decadron pre-medication as per institutional practice.

5.3.5 Monitoring of dose administration

Each patient will be monitored for vital signs and assessed for symptoms by the chemotherapy nurse before, during and after administration of treatment as per institutional guidelines.

5.3.6 Accountability and dispensation

Accountability and dispensation of doxorubicin and cyclophosphamide will follow oncology pharmacy policy for routine chemotherapy.

5.3.7 Disposition of unused drug

Disposition of doxorubicin and cyclophosphamide will follow oncology pharmacy policy for routine chemotherapy.

6. TREATMENT PLAN

6.1 Subject enrollment

Patients will be enrolled sequentially into this open-label, non-randomized phase I/II study. The phase I portion of the trial will include 2 dose levels, described in Section 6.2 and 6.3.

Patients will be enrolled into the phase II portion of the trial after the MTD/RP2D has been determined.

6.2 Dosage and Administration

MEDI4736 will be administered at two dose levels of either 3 mg/kg (1st dose level) or 10 mg/kg (2nd dose level) over 60 minute IV infusion every 2 weeks during the Phase I portion of the trial to establish the RP2D which will be used in the Phase II portion of the trial.

MEDI4736 will be administered immediately after administration of Nab-paclitaxel 100 mg/m^2 IV on Day 1 of chemotherapy on weeks 1, 3, 5, 7, 9, 11 (every two weeks). Nab-paclitaxel will be administered on day 1 weekly x 12 treatments.

After completion of the 12 courses of nab-paclitaxel / MEDI3476, doxorubicin and cyclophosphamide (AC) will be administered at 60 mg/m^2 and 600 mg/m^2 dose respectively, once every two weeks x 4 treatments as described in section 5.2. Pegfilgrastim 6 mg will be given as IM injection 24 hours (Day 2) after each AC chemotherapy. MEDI4736 is administered at the R2PD (or assigned dose cohort in the phase I portion) on Day 2 immediately after the administration of pegfilgrastim during each course of AC (weeks 13,15,17 and 19).

6.3 Dose Escalation Decision Rules

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.

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 patient 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.

Phase II portion of the trial

The interim efficacy and toxicity analysis will be performed after the first 22 two patients have completed chemotherapy therapy, undergone surgery and are eligible for efficacy assessment. Patients are eligible for efficacy assessment if they received at least 12 weeks of MEDI4736 at the recommended phase 2 dose concomitant with chemotherapy. Patients who received lower than the RP2D during the Phase I portion of the trial will not be included in the efficacy analysis. Patients who discontinued MEDI4736 within 12 weeks of initiation of therapy for any reason are also not eligible for efficacy analysis, but will be included in the toxicity assessment. Trial accrual will continue while efficacy and toxicity data is accumulating for the 22 patients.

The trial will terminate for lack of efficacy if < 7 patients out of the first 22 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 patients are accrued.

Safety analysis: If > 2/22 patients experience DLT or a serious treatment related adverse event (SAE) during the full 20 week treatment period, the MEDI4736 dose schedule will be re- evaluated. If futility criteria is not met (i.e. >7/22 patients have pCR), 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%.

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

If ≥20 patients 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%.

6.4 Definition of DLT

Dose limiting toxicities (DLT) to establish RP2D will be evaluated during the entire 20 weeks of therapy. Any DLT encountered during the 20 week treatment period will be considered DLT. Grading of toxicities will be according to NCI CTCAE v5.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/). The following toxicities will be considered DLT that require permanent discontinuation of MEDI4736:

- Any Grade 4 immune-mediated adverse event (imAE) defined as adverse events (AEs) of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will need to be performed to confirm a significant laboratory finding prior to designating it as a DLT.
- Any ≥ Grade 3 colitis irrespective of duration
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 or greater pneumonitis that does not resolve to ⩽ Grade 1 within 3 days of the initiation of maximal supportive care.
- Any Grade 3 imAE, (except colitis or pneumonitis, see above), that does not resolve to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ⩽ Grade 1 or baseline within 14 days.
- Any ⩾ Grade 3 non-imAE deemed by the treating physician to be probably causally related to MEDI4736 except those listed below which are NOT considered dose limiting:
    - Grade 3 fatigue lasting ⩽ 7 days
    - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
    - Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
    - Concurrent vitiligo or alopecia of any AE grade

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

6.5 Dose Modification and Toxicity Management

6.5.1 MEDI4736

For adverse events (AEs) that are considered at least partly due to administration of MEDI4736 the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of MEDI4736 along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for MEDI4736 (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued.

Following the first dose of MEDI4736, subsequent administration of MEDI4736 can be modified based on toxicities observed (see Table 1, 2, and 3 below).

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing immune mediated Adverse Events (imAEs) during the conduct of this study. Potential imAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Tables 1, 2, and 3, respectively.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3.

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Table 1 - Dosing modification and toxicity management guidelines for immune-mediated reactions associated with MEDI4736

	Dose Modifications	Toxicity Management
Immune-related Adverse Events (Overall Management For toxicities not noted below)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks of the start of immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced Grade 3 treatment-related imAE following resumption of dosing Grade 1: No dose modification Grade 2: Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent	It is recommended that management of immune-mediated adverse events (imAEs) follow the guidelines presented in this table: – It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day PO or IV equivalent – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of

Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formally known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient.
Grade 4	Permanently discontinue study drug/study regimen Note: For Grade ≥3 asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should	

	be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade ‹1 upon treatment with systemic steroids and following full taper. Note: There are some exception to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	

Pediatric Considerations

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of the start of the immune-mediated event (imAE)**	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	Any Grade	General Guidance	For Any Grade: – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider Pulmonary and Infectious Disease consults
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab

			– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections[1] – Consider Pulmonary and Infectious Disease Consults – Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening) – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections[a]
Diarrhea/ Colitis **Large intestine perforation/Intestine perforation**	Grade of Diarrhea (CTCAE version 5.0)	General Guidance	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) – Steroids should be considered in the absence of clear alternative etiology, even for

[1] ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

			low grade events, in order to prevent potential progression to higher grade event, including perforation – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only, intervention not indicated)	No dose modification	For Grade 1: - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.

	Grade 2 (Diarrhea: stool frequency of 4-6 over baseline per day; intervention not indicated) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then study drug/study regimen can be resumed after completion of steroid taper	For Grade 2: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[2]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.[a]

[2] ASCO Educational Bcatook 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

	Grade 3 or 4 diarrhea (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)	Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. Grade 4 Permanently discontinue study drug/study regimen.	For Grade 3 or 4: - Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). - Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	For Grade 1: – Continue LFT monitoring per protocol.

	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1, resume study drug/study regimen after completion of steroid taper.	For Grade 2: – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workupwork up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	Grade 3 or 4 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal) (Grade 4: (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	Grade 3: For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For evaluations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] For Grade 4: Permanently discontinue study drug/study regimen.	For Grade 3 or 4: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Hepatitis (elevated LFTs) Infliximab should not beused for management of immune-related helpatitis. See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	Any Grade	General Guidance	For Any Grade: – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – onsider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBC viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
		•	
	(Isolated AST or ALT >ULN and <5.0 x ULN, whether normal or elevated at baseline.	• No dose modifications • If ALT/AST elevations represents significant worsening based n investigator assessment, then treat event as described for elevations in the row below. For all transaminase elevations, see	

		instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in stetting of either increasing bilirubin or signs of DILI/liver decompensation	
	(Isolated AST or AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used.

	(Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections). [a]
	(Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	For Grade 4: Same as above (except would recommend obtaining liver biopsy early)
If transaminase rise is not isolated (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise - For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)			

- For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen			
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Any Grade	General Guidance	For Any Grade: – Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptoms • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.

	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold study drug/study regimen until resolution to Grade ≤ 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤ 1 or baseline then resume study drug/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections) [a]. – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	For Grade 3 or 4: – Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections. [a]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCI CTCAE version 5.0 for definition of	General Guidance	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL**

	severity/grade depending on type of skin rash)		**NECROLYSIS.****
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper	For Grade 2 : – Obtain Dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4 (or life-threatening): – Consult Dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider, as necessary, discussing with Study Physician
	Grade 4 (or life-threatening)	Permanently discontinue study drug/study regimen	

Endocrinopathy (e.g., hyperthyroidism, thyroiditis, Type 1 diabetes mellitus, hypophysitis, hypothyroidism, hypopituitarism, adrenal insufficiency, exocrine event of amylase/lipase increased also included in this section)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity)	General Guidance	– Consider consulting an Endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	For Grade 2: (including those with symptomatic endocrinopathy) – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections.[a] – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 5.0 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insuffiency) can be retreated wth study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are <10 mg/day or equivalent.	For Grade 3 or 4: – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – or adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic	**Andy Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the	**General Guidance**	For Any Grade: – Patient should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior

neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	CTC grade/severity)		change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve condition investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications	**For Grade 1:** See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3 or 4	**For Grade 3:** Hold Study drug/study regimen dose until resolution to Grade ≤ 1 Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG)

		For Grade 4: Permanently discontinue study drug/study regimen	– Once stable, gradually taper steroids over ≥28 days
Peripheral neuromotor syndromes (such as Guillain-Barre and Myasthenia Gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic	No dose modification	**For Grade 1:** – Consider, as necessary, discussing with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult

	observations only; intervention not indicated)		
	Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	Hold study drug/study regimen dose until resolution to Grade ≤ 1 Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	**For Grade 2:** – Consider, as necessary, discussing with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL;	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤ 1 Permanently discontinue study	**For Grade 3 or 4 (severe or life-threatening events):** For severe or life threatening (Grade 3 or 4) events: – Consider, as necessary, discussing with study physician. – Recommend hospitalization

	Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability **For Grade 4:** Permanently discontinue study drug/study regimen.	– Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG
	Grade 4	Permanently discontinue study drug/study regimen	
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician.

			– Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic interventions only; intervention not indicated(treat myocarditis with mild symptoms as Grade 2)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 2-4:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4	If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade	**For Grade 2-4:** – Monitor symptoms daily, hospitalize.

	(Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms) (Grade 4: Life threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	– Promptly start IV methylprednisolone 2 to 4mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections.[a]
Myositis / Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.

			− If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the study physician. − Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	No dose modifications.	**For Grade 1:** − Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. − Consider Neurology consult. Consider, as necessary, discussing with the study physician.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve	**For Grade 2:** − Monitor symptoms daily and consider hospitalization. − Obtain Neurology consult, and initiate evaluation. − Consider, as necessary, discussing with the study physician.

		to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	– If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections.[a]
	Grade 3 or 4 Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis.

			Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections.[a]

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Table 2 - Dosing modification and toxicity management guidelines for infusion-related reactions associated with MEDI4736		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Non-immune Mediated Reactions **(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"**		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Abbreviations:

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; imAE = immune-mediated adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[ib] NCI CTCAE version 5.0

6.5.2 Nab-paclitaxel

Nab-paclitaxel dose will be reduced for

- Grade 3 peripheral neuropathy (i.e. sensory alteration or paresthesia interfering with normal daily activities); treatment with nab-paclitaxel will be held for a maximum of 14 days. If symptoms improve within this time period to grade 2 or less, resume nab-paclitaxel at 80 mg/m^2 dose. If neuropathy does not resolve to grade 2, discontinue nab-paclitaxel and start the doxorubicin/cyclophosphamide phase of the treatment.

- Absolute neutrophil count (ANC) is below < 1000/microliter or platelet count < 100,000/microliter on the day of chemotherapy administration, nab-paclitaxel should be held and complete blood count repeated 24 hours later. Resume administration of nab-paclitaxel at full dose once ANC >1000 and Plt > 100,000. Use G-CSF with subsequent treatments to prevent dose delays should follow NCCN practice guidelines (18).

6.5.3 Dose dense doxorubicin/cyclophosphamide (ddAC)

The dose of doxorubicin/cyclophosphamide will be reduced for

- Absolute neutrophil count (ANC) is below < 1000/microliter or platelet count < 100,000/microliter on the day of chemotherapy administration, ddAC should be held and complete blood count repeated 24 hours later. Resume administration of ddAC at 20% reduced dose for both drugs for all subsequent cycles.

6.5.4 Toxicity management guidelines for combination treatment regimen

MEDI4736 and nab-paclitaxel or doxorubicin and cyclophosphamide are not expected to have overlapping toxicities other than fatigue and nausea. These side effects, as well as all other chemotherapy related side effects, will be managed following routine clinical practice (i.e. antiemetics, growth factors, dose delays and dose reductions as described in sections 6.5.1-3).

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

Contraception must be practiced

Non-sterilised male patients who are sexually active with a female partner of childbearing potential and female patients of childbearing potential who are sexually active with a non-sterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 6 months after the final dose of MEDI4736 and AC chemotherapy. Females of childbearing potential are those who are (i) not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or (ii) postmenopausal defined as 12 months with no menses without an alternative medical cause.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- All subjects, male or female, with childbearing potential as defined above must use a combination of two acceptable methods of effective contraception. Effective methods of contraception are listed in Table 4.

Table 4. Effective methods of contraception (a combination of two methods must be used)

Barrier Methods	**Intrauterine Device Methods**	**Hormonal Methods**
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)	Combined pill Minipill Patch

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of MEDI4736.

7.2 Concomitant treatment(s)

7.2.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 7.2.2.

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies

2. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated combination regimens.

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

4. Live attenuated vaccines within 30 days of MEDI4736 dosing (ie, 30 days prior to the first dose, during treatment with MEDI4736 and for 30 days post discontinuation of MEDI4736). Inactivated viruses, such as those in the influenza vaccine, are permitted.

8. STUDY PROCEDURES

8.1 Schedule of study procedures

Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

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8.1.1 Screening Phase

Within 6 weeks of study entry:

1. Assessment of the primary tumor with bilateral mammograms and if clinically indicated also with ultrasonograms or MRI to determine the clinical T and N stage of the disease. The most recent breast imaging that provides tumor size estimate has to be within 12 weeks of study entry.

2. If the tumor is less than 2 cm, the tumor site will need to be identified with radiopaque marker via ultrasound guidance or tattooing of the skin before starting treatment. This procedure is not necessary for patients who have microcalcifications in the breast corresponding to the tumor.

3. Obtain 3 core needle biopsies for correlative science studies and blood collection for research (5 ml blood will be collected into 1 red-top and 1 green-top tube respectively)

4. Systemic staging should follow standard NCCN practice guidelines as appropriate for clinical stage (Theriault et 2013).

5. Female patients with childbearing potential or must have a negative urine or serum pregnancy test upon study entry.

Within 14 days of starting therapy:
NOTE: If any of the bellow laboratory assessments are abnormal at time of screening but still within the ranges allowed for edibility, these tests will need to be repeated on Day 1 before treatment could commence.

6. Complete blood count and differential

7. serum creatinine, creatinine clearance

8. total bilirubin, AST , ALT

9. PT, PTT, INR

10. TSH (free T4 if TSH is elevated)

11. Patients with elevated liver functions or clinical symptoms or history of hepatitis will also have hepatitis panel (e.g. HAV Ab; HBsAb; HBsAg; HBcAb; HCV Ab) to rule out acute hepatitis.

12. ECG (x 3 reads within 5 minutes)

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Within 7 days of starting therapy

13. Complete physical examination

14. Review of all systems and medical history

15. Patients of childbearing potential must also have urine pregnancy test within 7 days of starting therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required for confirmation.

8.1.2 Treatment Phase

During neoadjuvant therapy patients must be assessed as follows:

Weekly before each Nab-paclitaxel therapy and every two-weeks before each AC chemotherapy:

1. Complete blood count and differential (as per institutional chemotherapy orders)

2. Nursing assessment as per institutional protocol

Every Two weeks (before each MEDI4736 treatment):

1. All patients must be seen by the treating physician or advance practice nurse every 2 weeks during the treatment (i.e. on the day or 1-2 days before administration of therapy).
   a. Complete history, review of systems and physical exam must be performed including clinical tumor measurements. Patients will be monitored for clinical symptoms of immune-mediated adverse reactions including enterocolitis, dermatitis, hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy, and development of serious infection, infusion related reactions, hypersensitivity reactions.
   b. Toxicity will be graded following the NCI CTCAE version 5.0 criteria. The full text is available online at: (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/)
   c. If during therapy the tumor becomes no longer palpable because of response, it is recommended that the tumor site is marked with radiopaque marker via ultrasound guidance. This procedure is not necessary for patients who have microcalcifications in the breast corresponding to the tumor or already have markers placed before starting therapy.
   d. Breast imaging may be repeated any time during therapy if clinically indicated for suspicion of progression.

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Once every 4 weeks (+/- 1 week) after starting therapy and whenever clinically indicated:

1. Serum creatinine, total bilirubin, AST, and ALT.
2. Serum TSH and if TSH is elevated free T3 and T4.
3. Urinalysis

ECGs (single trace) will be repeated on week 6 (+/- 1 week) during the Nab-paclitaxel therapy and on week 17 (+/- 1 week) during the AC part of the chemotherapy.

After completion of all preoperative chemotherapy but before surgery

1. Repeat blood collection for research will be performed 2 weeks (+/- 1 week) after completion of the last dose of neoadjuvant therapy (5 ml blood will be collected into 1 red-top and 1 green-top tube respectively).

Surgery:

It is recommended that surgery be performed within 4 weeks of completion of the last chemotherapy unless medical contraindications exist. Surgical resection of the tumor bed and axillary sampling should follow standard clinical practice.

In patients who have residual invasive cancer, 10 FFPE sections (5 micron each) will be collected for correlative science studies after routine pathology examination of the surgical specimen is completed.

Post-treatment follow-up:

Three delayed toxicity assessments will be performed after completion of neoadjuvant therapy. Each visit will include complete medical history, toxicity assessment, physical examination and serum AST, ALT, total Bilirubin and complete blood count assessment.

The first is 2 weeks (+/- 1 week) after completion of the last MEDI4736 therapy.

The second, at 6 weeks (+/- 1 week) after completion of therapy (approximately 2 weeks after surgery).

The third is 13 weeks, approximately 90 days (+/- 14 days), after completion of therapy.

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Delayed toxicities will be reported separately from acute toxicities while on treatment and will not be included in the DLT assessment.

8.1.3 End of Treatment

End of treatment is defined as the last planned dosing visit prior to surgery.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

ECGs are required during screening, within 14 days prior to starting study treatment and will be repeated on week 6 (+/- 1 week) during the Nab-paclitaxel therapy and on week 17 (+/- 1 week) during the AC part of the chemotherapy, and may be repeated any time if clinically indicated. ECGs recorded during the screening period will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart); ECGs recorded during the treatment phase will be single tracing. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 8.1. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On MEDI4736 treatment days, vital signs will be measured within an hour prior to start of MEDI4736 administration, at 30 minutes during the infusion (± 5 minutes), at the end of

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infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then temperature, blood pressure, pulse rate, and respiratory rate measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses (at dose levels of 10 mg/kg or less), the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

8.2.2 Clinical laboratory tests

Section 8.1.1 and 8.1.2 lists screening and on-treatment laboratory tests that are required during the study.

Table 5 - Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular haemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 6 - Clinical chemistry (serum or plasma) Laboratory Tests

Alanine aminotransferase	PT
Aspartate aminotransferase	PTT
Creatinine	INR
Total bilirubin[b]	TSH

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

Table 7 - Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

8.3 Biological sampling procedures

Three pre-treatment core needle biopsies will be obtained and 10 x 5 micron FFPE sections of residual cancer tissues will be collected for correlative science research. Tissue samples will be stored de-identified and labelled with patient study ID number only in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT.

Blood collection for research

10 mL blood will be collected for future research before starting therapy and 2 weeks (+/- 1 week) after completion of all neoadjuvant therapy but before surgery. Blood samples will be labelled with de-identified patient study number and will be picked up by a laboratory personnel and stored in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT.

Estimate of volume of blood to be collected. The total volume of blood that will be drawn from each subject in this study is as follows:

Table 8 - Volume of blood to be drawn from each subject

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	**Clinical chemistry**	10 ml	5	50 mL
	Hematology	5 ml	20	100 mL
For Future Research		10 mL total (red- and green-top tubes, 5 mL each)	4 (samples at baseline and two samples after treatment)	20 mL
Total				170 mL

8.3.1 Fresh tumor biopsies before starting therapy

Three core needle biopsies of the cancer will be obtained for correlative science studies before starting the first course of therapy. Tissue collection will be performed by a breast surgeon (if the lesion is palpable) or by radiologist (for non-palpable lesions) or their designate following standard operating procedure for diagnostic biopsies.

a. 1 core biopsy sample will be placed into 1.5 ml plastic vials containing RNAlater™ (Qiagen). RNA later vial labeled with de-identified patient study number will be supplied by the Pusztai laboratory. The sample in RNAlater will be picked up by a laboratory personnel and stored in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT.

b. 1 biopsy sample will be placed in Corning 2 ml cryogenic vial and snap freeze in liquid nitrogen. The frozen sample will be picked up by a laboratory personnel and stored in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT.

c. 1 biopsy sample will be placed in formalin for fixation and will be embedded in paraffin following standard clinical operating procedure. Specimens will be labelled with de-identified patient study number and samples will be picked up by a laboratory personnel and stored in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT..

8.3.1.1 Tumor tissue from surgical resection

In patients who have residual invasive cancer, 10 FFPE sections (5 micron each) will be collected for correlative science studies to assess immune parameters and the genomic architecture of the cancer that survived therapy. The sections will be cut after completion of routine pathology assessment for pCR. Specimens will be labelled with de-identified patient study number and samples will be picked up by a laboratory personnel and stored in the Breast Cancer Translational Research Laboratory in room 786, 300 George St, New Haven, CT.

8.3.2 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. The Principal Investigator:

Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1.1 Pathologic Complete Response (pCR)

The primary efficacy endpoint is pathologic complete response (pCR). Pathologic response will be assessed in the surgically resected cancer and lymph nodes after completion of all chemotherapy by the local pathologist as part of routine care. Pathologic complete response is defined as no invasive cancer in the resected breast tissue and lymph nodes (ypT0/Tis, ypN0). This information will be extracted from the pathology report and patients will be assigned to one of two response categories, pCR or residual disease (RD) for the purpose of efficacy analysis.

10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

10.1.1 Safety Parameters

10.1.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

10.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect in offspring of the subject

Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

10.1.3 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is an event of scientific and medical interest specific to the further understanding of the MEDI4736 safety profile and require close monitoring and rapid communication by the investigator to the sponsor. MEDI4736 AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

MEDI4736, an anti-PD-L1 antibody, and belongs to a new class of anticancer therapies, called “checkpoint-inhibitors” that amplify antitumor immune responses by blocking inhibitory signaling pathway modulated by the co-inhibitory or co-stimulatory receptors, CTLA-4 and PD-1, expressed on T cells (Callahan and Wolchok, 2013). This class of drugs can have a wide spectrum of immune-mediated reactions that have been considered inflammatory in nature and can affect any organs of the body.

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis

- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforations

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

10.1.3.1 Pneumonitis

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of off-target effects of checkpoint inhibitors against the normal lung parenchyma. (Chow, 2013) Presentations of pneumonitis range from asymptomatic lung infiltrates to a mimic of severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia.

The frequency of immune-mediated pneumonitis in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 4%. (Topalian et al, 2012; Brahmer et al, 2012)

Because pneumonitis can quickly escalate and become fatal, early recognition is essential. Initial workup includes chest imaging; however, pneumonitis can have highly variable appearances on chest CT scans. In patients with pulmonary metastases or cardiopulmonary comorbidities, evaluation can be particularly challenging as it can be difficult to differentiate between infection, early pulmonary edema, alveolar hemorrhage, immune-mediated pneumonitis, immune-related tumor inflammation, and tumor progression (Topalian et al, 2012). Pneumonitis has also been reported as a complication of cancer treatment associated with lung and breast cancer.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section 6.6.1.

10.1.3.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Topalian et al, 2012; Brahmer et al, 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 6.6.1.

10.1.3.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 6.6.1.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

10.2 Assessment of safety parameters

The safety evaluation period during this study extends from date of first treatment until 90 days after completion of therapy with MEDI4736 or until resolution from all acute toxicities associated with the drug administration.

10.2.1 Assessment of severity

There is a distinction between serious and severe AEs. Assessment of seriousness will be made solely by the serious criteria listed above. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea which persists for several hours. This would be classified as a "severe" episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v5.0. If a certain event or symptom is not described in the CTCAE grades, use the following grading scale:

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	Any adverse drug experience that places the patient or patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death.
Grade 5 (fatal)	Death (loss of life) as a result of an event.
Unexpected AE	Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

10.2.2 Assessment of relationship

Determination of causality between an adverse event and drug therapy will be made after consideration of all clinically relevant data prior to, during, and after occurrence of the event. Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered. An adverse event is associated with the use of the drug when there is a reasonable possibility that the drug may have caused the event.

The following attribution guidelines are recommended by the US National Cancer institute:

Unrelated: The Adverse Event is clearly not related to the investigational agent (s)

Unlikely: The Adverse Event is doubtfully related to the investigational agent(s)

Possible: The Adverse Event may be related to the investigational agent(s)

Probable: The Adverse Event is likely related to the investigational agent(s)

Definite: The Adverse Event is clearly related to the investigational agent(s)

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

AE (verbatim)
The date and time when the AE started and stopped
Changes in NCI CTCAE grade and the maximum CTC grade attained
Whether the AE is serious or not
Investigator causality rating against MEDI4736 (yes or no) and against combination drug (yes/no)
Action taken with regard to MEDI4736/comparator/combination agent
Outcome

In addition, the following variables will be collected for SAEs as applicable:
Date AE met criteria for serious AE
Date Investigator became aware of serious AE
AE is serious due to
Date of hospitalization
Date of discharge
Probable cause of death
Date of death
Autopsy performed
Description of AE
Causality assessment in relation to Study procedure(s)
Causality assessment in relation to Additional Study Drug

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (including a minimum of 90 days after the last dose of MEDI4736).

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with MEDI4736. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Yale Principal Investigator SAE Reporting Requirements

The principal investigator (PI) will assess all expedited adverse events and will periodically review all adverse events observed on the trial. The PI will promptly investigate all safety information related to an adverse experience. If the results of the PI's investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is reportable, the PI will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

Yale Safety Reporting And Monitoring (DSMP)

The PI will monitor the clinical trial for safety and follow the Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events. These procedures are in compliance with federal regulations; 21 CFR 312.32 and 312.22. The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into OnCore computerized clinical trial database by Yale Cancer Center Clinical Trials Office personnel trained in clinical trial data management.

The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Data Safety Monitoring Board (DSMB). Safety data will be submitted to the DSMB at least once yearly or more often as required by the DSMP. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across all patients. Regular meetings among the study team are held to discuss ongoing patient treatment and adverse events.

Expedited SAE reports are copied to the Human Investigations Committee (HIC) within the timeframes required by Yale. The PI and designated personnel will distribute manufacturer-provided safety reports and updated Toxicity Lists to the institution's HIC and all relevant personnel involved in the conduct of the study. The Toxicity List, in addition to the Investigator's Brochure, will be used as a reference for reporting any new SAE.

Reporting of SAE to the Yale Human Investigation Committee

All SAEs, whether originating at Yale or a collaborating center, meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 6A within 48 hours of discovery.

The HIC expedited reporting criteria are:

a. Serious AND unexpected AND possibly, probably or definitely related events;

b. Anticipated Adverse Events occurring with a greater frequency than expected.

The HIC does not require reporting of any other Adverse Event type. A copy of the HIC reporting policy is available at http://info.med.yale.edu/hic/policy/AdverseEventPolicy.pdf

Reporting of SAE to the FDA and AstraZeneca

The sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

"Notification from an Investigator Sponsored Study"

The investigator IND number assigned by the FDA

The investigator's name and address

The trial name/title and AstraZeneca reference number (ESR-14-10265)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:***
AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.3.2.1 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of MEDI4736 safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of MEDI4736 safety follow-up period will be documented but will not be reported as an SAE.

10.3.3 Other events requiring reporting

10.3.3.1 Overdose

An overdose is defined as a subject receiving a dose of MEDI4736 in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with MEDI4736, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization,

the event is serious and must be recorded and reported as an SAE (see Section 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of MEDI4736.

The investigator will use clinical judgment to treat any overdose.

10.3.3.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

10.3.3.3 Pregnancy

Pregnancy itself, or pregnancy of a subject's partner, is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of any conception occurring from the date of the first dose until 90 days after the last dose (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study.

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 for contact information).

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.

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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.

12.5 Audits and inspections

This study will be monitored by the Yale Clinical Trial Office and Yale Data Safety Monitoring Committee.

13. STUDY MANAGEMENT

The Principal Investigator Dr Lajos Pusztai will oversee all aspects of the conduct of this trial. Data collection, study monitoring and management of the trial will be provided by the Yale Cancer Center Clinical Trial Office Breast Cancer Disease Team.

13.1 Training of study site personnel

All clinical trials conducted at Yale Cancer center are supported by a central Clinical Trial Office (CTO). The CTO employs, trains and supervises all clinical trial assistants, research nurses, regulatory assistants, data managers. The CTO staff is organized into disease units. The breast CTO staff includes two research nurses, two data managers, a regulatory assistant, trial assistant and a project manager. Staffing of disease teams is dynamic and may change based on the needs of the disease unit. Further information on the CTO can be found at: http://www.yalecancercenter.org/research/trials/services/index.aspx.

Barbara Fordyce serves as project manager for the breast cancer disease group, e-mail: Barbara.fordyce@yale.edu, telephone: 203-737-2226.

13.2 Monitoring of the study

13.2.1 Source data

Source data is the electronic medical record system of Smilow Cancer Hospital.

13.3 Study timetable and end of study

The anticipated completion of accrual to the Phase I portion of the trial is 6-9 months due to 20 week observation period for each dose escalation cohort. Full accrual to the Phase II portion will take an additional 20-24 months assuming an accrual rate of 2 per months.

Final efficacy analysis will be reported 6 months after accrual of the last patient to the Phase II portion of the trail.

14. DATA MANAGEMENT

Source data will be collected in the clinic by a research nurse dedicated to the trial and the information will be entered into an electronic data bases, ONCORE, by a trained data manager/clinical trial assistant. The data elements and case report forms will be designed by the principal investigator following the policy of the Clinical Trial Office. The ONCORE datadase will be used to generate reports.

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APPENDIX A: MEDI4736 DOSE CALCULATIONS

MEDI4736 Dosing

The MEDI4736 dosing should be done depending on subject weight:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL) where 50 mg/mL is MEDI4736 nominal concentration

The corresponding volume of MEDI4736 should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 80 kg

3. Dose for subject: 800 mg = 10 (mg/kg) × 80 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 800 mg / 50 (mg/mL) = 16.0 mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 16.0 (mL) / 10 (mL/vial) = 2 vial