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Protocol PI	Clinton Yam
Department	Breast Medical Oncology
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Triple-Negative First-Line Study:

Neoadjuvant trial of nab-paclitaxel and Atezolizumab (MPDL3280A), a pdl-1 inhibitor in patients with triple negative breast cancer.

Study Chair: Clinton Yam, MD
Assistant Professor Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center

Collaborators:

W. Fraser Symmans, MD
Professor, Pathology
The University of Texas MD Anderson Cancer Center

Jennifer K. Litton, MD
Professor, Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center

Debu Tripathy, MD
Chair, Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center

Lumarie Santiago, MD
Associate Professor, Department of Diagnostic Radiology - Breast Imaging
The University of Texas MD Anderson Cancer Center

Rosalind Candelaria, MD
Assistant Professor, Department of Diagnostic Radiology – Breast Imaging
The University of Texas MD Anderson Cancer CenterGaiana Margishvili Rauch, MD PhD
Associate Professor, Department of Diagnostic Radiology – Breast Imaging
The University of Texas MD Anderson Cancer Center

Beatriz Elena Adrada, MD
Associate Professor, Department of Diagnostic Radiology – Breast Imaging
The University of Texas MD Anderson Cancer Center

Kristofer Jennings, PhD
Assistant Professor, Department of Biostatistics
The University of Texas MD Anderson Cancer Center

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ATA	Antitherapeutic antibody
AST	Aspartate aminotransferase
BCS	Breast conserving surgery
CMP	Comprehensive metabolic panel
CRC	Colorectal cancer
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DFS	Disease-free survival
ECG	Electrocardiogram
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
IRB	Institutional review board
IND	Investigational new drug
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hormone receptor
IV	intravenous(ly)
IRB	Institutional Review Board
LFT	Liver function test
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NK	Natural Killer
NACT	Neoadjuvant chemotherapy
NSCLC	Non-small cell lung cancer
OS	Overall survival
pCR	Pathologic complete response
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetics
PR	Progesterone receptor
PD-L1	Programmed death ligand 1
PD-1	Programmed death 1
RCC	Renal cell carcinoma
RCB	Residual cancer burden
RD	Residual disease
SAE	Serious adverse event
TNBC	Triple negative breast cancer
TIL	Tumor infiltrating lymphocyte
TSH	Thyroid stimulating hormone

1.0 STUDY SUMMARY

Abbreviated Title	Ph 2 of atezolizumab plus Nab-Paclitaxel in TNBC
Study Phase	Phase 2
Clinical Indication	TNBC
Route of administration	IV
Accrual Goal	37
Estimated duration of enrollment	24 months
Duration of Participation	3 years, 6 months on active therapy

2.0 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective & Hypothesis

To evaluate the rate of pathologic complete response (pCR)/RCB-0 + residual cancer burden (RCB)-I responses in patients with triple negative breast cancer (TNBC), who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, treated with atezolizumab in combination with nab-paclitaxel in the neoadjuvant setting. Pathologic complete response will be defined as no residual invasive disease in the breast or regional lymph nodes.

Hypothesis:

(1) Among patients with TNBC who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, the combination of atezolizumab and nab-paclitaxel administered in the neoadjuvant setting will increase pCR and RCB-I rates.

2.2 Secondary Objectives & Hypotheses

1. To estimate Progression Free Survival (PFS) distribution of TNBC patients who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, treated with atezolizumab in combination with nab-paclitaxel in the neoadjuvant setting.

2. To determine the safety of atezolizumab in combination with nab-paclitaxel in the neoadjuvant setting

Hypotheses:

(1) Among patients with TNBC who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, the combination of atezolizumab and nab-paclitaxel administered in the neoadjuvant setting will increase 3-year DFS distribution.

(2) The combination of atezolizumab and nab-paclitaxel will be safe in TNBC patients.

2.3 Exploratory Objective

(1) To investigate the association between biomarkers in the peripheral blood and tumor tissue with efficacy for TNBC patients treated with atezolizumab in combination with nab-paclitaxel in the neoadjuvant setting.

3.0 BACKGROUND & RATIONALE

3.1 Background

3.1.1 Overview of Triple Negative Breast Cancer

TNBC is a subtype of invasive breast cancer that lacks estrogen receptor (ER), progesterone receptor (PR) and HER2 expression. TNBC has an especially poor prognosis in patients whose tumor does not respond to anthracycline and taxane-based chemotherapy. As a subset of breast cancer, TNBC is especially challenging to treat due to its heterogeneity as these tumors are grouped together only because of their lack of ER, PR and HER2 expression. In a study by Lehman, et al, by using gene expression profiles, 6 subtypes of TNBC have emerged each with its own intrinsic biology and likely responsiveness to therapy.[1] To date there are no targeted therapies for TNBC, therefore chemotherapy remains the mainstay of treatment. Data in the neoadjuvant (preoperative) setting shows that patients with TNBC have a higher sensitivity and pCR rate to standard systemic chemotherapy than do patients with other subtypes of breast cancer, such as endocrine sensitive cancers.[2,3] However, for those patients that do not obtain a pCR or minimal residual cancer burden (RCB-I), their survival outcomes are significantly worse.[4] Therefore measuring the response to chemotherapy and quantifying the residual disease by the RCB method yields important prognostic information, identifying patients who may benefit from additional therapy as part of a clinical trial (please see below, section 9.3 for a complete description of assessing for RCB).

3.1.2 Neoadjuvant Chemotherapy: Historical Perspective

Since its initial use in the early 1970s, neoadjuvant chemotherapy (NACT) has become the standard of care for management of locally advanced breast cancer and inflammatory breast cancer. [5-7] It has since been used increasingly for the treatment of early-stage breast cancer. Preclinical observations[8,9] and mathematical models of tumor growth, dissemination, and development of resistance to chemotherapy support the use of NACT. In addition, the available data suggest that use of NACT could lead to improved DFS and overall survival (OS) rates, presumably through early treatment of systemic micrometastatic disease. NACT also provides several advantages, including providing an early surrogate marker (pCR), for long-term outcome.[4] As pCR has been demonstrated to correlate with long term DFS and OS, it has recently been identified as an appropriate endpoint for Food and Drug Administration (FDA) approval pathways in breast cancer. Other purported advantages of NACT include: 1) down-staging allowing surgery for non-operable breast cancer, and increasing breast-conserving surgery (BCS) rates in patients with large operable tumors, 2) providing an in-vivo model to assess response to therapy, and 3) serving as a research tool for understanding breast cancer biology and treatment mechanisms of action.

3.1.3 Pathologic Assessment after NACT

A variety of endpoints can be used to measure outcomes in trials evaluating NACT for breast cancer other than directly measuring survival (DFS and OS), which requires a large number of patients and long term follow-up. These endpoints include clinical response, radiologic response, rate of BCS, and pathologic response. The results of several studies have been shown that pCR (for the purposes of this study defined as no residual invasive cancer in the breast or regional lymph nodes) is predictive of long-term survival.[2,4,6,9] Attainment of pCR is associated with a favorable prognosis, with patients attaining a pCR having a lower risk of subsequent recurrence and improved OS compared with patients with residual invasive tumor.

Symmans et al. showed a continuous index combining pathologic measurements of the primary tumor (size and cellularity) and nodal metastases (number and size) is an independent predictor of distant relapse-free survival.[10] Patients with minimal residual disease (RD) (RCB-I) carried the same prognosis as pCR (RCB-0). On the other hand, patients with extensive RD (RCB-II/III) had poor prognoses. RCB was independently prognostic in a multivariate model that included age, pretreatment clinical stage, hormone receptor (HR) status, hormone therapy, and pathologic response (pCR vs. RD; hazard ratio = 2.50; 95% CI 1.70 to 3.69; P < .001). Seventeen per cent of patients had minimal RD (RCB-I). Extensive RD (RCB-III) was seen in 13% of patients. RCB-III was associated with poor prognosis, regardless of HR status, adjuvant hormone therapy, or pathologic American Joint Committee on Cancer stage of residual disease. The calculation formula and detailed description of the RCB can be found at a dedicated Web site: http://www.mdanderson.org/breastcenter_RCB.

Given the fact that patients that achieve a pCR (RCB-0) or have minimal RD (RCB-I) have the same excellent prognosis, evaluating the combination of these outcomes in patients who had previously not shown significant response to NACT makes biological sense as a combined outcome measure when novel therapeutics or therapeutic strategies are being investigated in the neoadjuvant setting.

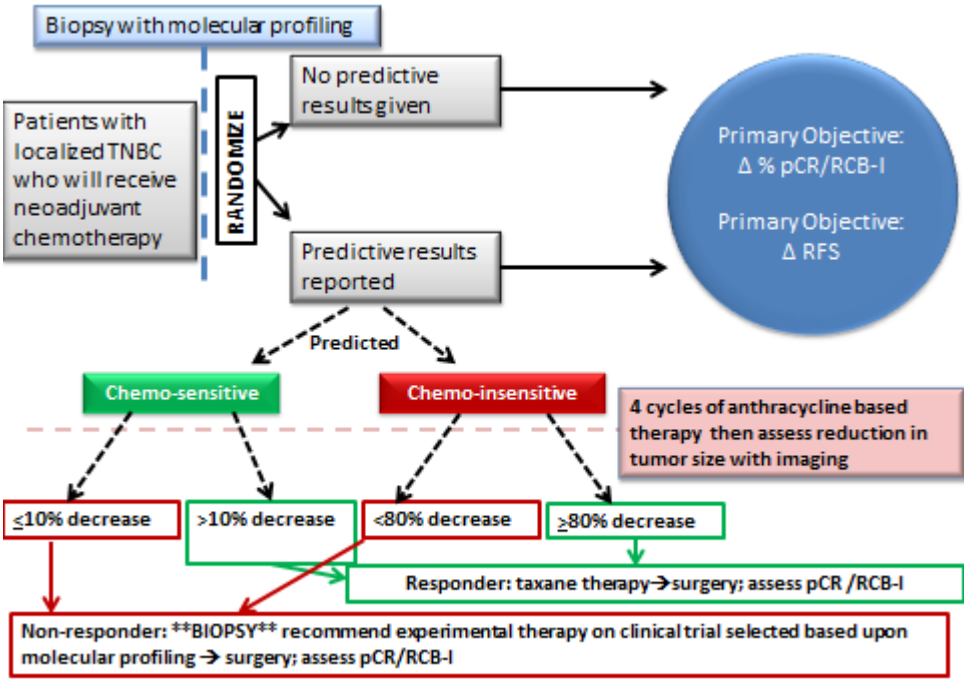
3.1.4 MD Anderson Cancer Center TNBC Triaging Protocol (MDACC 2014-0185)

Approximately 50% of patients with TNBC treated with standard taxane/anthracycline-based NACT will have either pCR (RCB-0) or minimal RD (RCB-I) at the time of surgical resection. Those patients have identical and exceptionally good long-term prognosis (less than 10% risk of developing distant metastatic disease within 5 years). Unfortunately, those with more extensive RD (RCB-II/III) have a much worse prognosis, with more than 50% of patients developing distant metastatic disease within 5 years of initial diagnosis.[4]

Clinical trials of NACT in breast cancer have demonstrated that patients without response to their first chemotherapeutic regimen have a low chance (5%) of achieving pCR after their second neoadjuvant chemotherapy regimen. However, this has not been the case with targeted regimens such as trastuzumab in HER2+ tumors, suggesting that intrinsic resistance to chemotherapy can be overcome with appropriate targeted therapy.[11] Though several novel agents have been tested for treatment in TNBC, so far none have been successful. It has been proposed that this might be due to the molecular heterogeneity of tumors classified within the “catch all” category of TNBC.

Given the disparity of treatment outcomes from NACT for TNBC, this parent protocol (MDACC 2014-0185) is a diagnostic platform to identify patients whose tumors are likely or unlikely to achieve pCR or RCB-I, in order to direct predicted responders toward standard chemotherapy and to direct predicted chemotherapy insensitive patients toward potentially more effective experimental therapies within clinical trials. This will be done with 2 methods. The first is radiographic evaluation of the tumor to measure response. The second is using a molecular predictor of sensitivity to neoadjuvant/adjuvant systemic therapy for clinical Stage II-III breast cancer that is independently associated with excellent distant recurrence-free survival in those predicted to have chemotherapy-sensitive disease (HR+/HER2- or TNBC) developed at MDACC by Dr. Symmans and colleagues. This predictor has been described more fully in the parent protocol (see appendix G of this trial). Retrospective validation studies have been completed to support the use of this genomic testing to molecularly triage therapy for patients with localized breast cancer.

The study schema for the parent triaging protocol is below:



3.1.5 Immunotherapy and Breast Cancer

Immunotherapy is a rapidly evolving field for the treatment of breast cancer, specifically TNBC. Studies have shown that tumor-infiltrating lymphocytes (TIL) have both prognostic and predictive significance in TNBC patients. TIL as a positive prognostic biomarker was first reported using baseline samples from the phase III BIG02-98 adjuvant therapy trial investigating the addition of docetaxel to anthracycline in node-positive breast cancer. [12] TIL were evaluated on hematoxylin & eosin stained sections and for each 10% increase in intratumoral and stromal TIL, there was a 17% and 15% reduced risk of relapse and 27% and 17% reduced risk of death respectively. The significance of stromal TIL was recently confirmed in TNBC samples collected during two Eastern Cooperative Oncology Group (E2197 and E1199) adjuvant therapy trials. [13] The presence of TIL have also been shown to have predictive value with the presence of TIL being associated with higher pCR rates independent of other clinicopathologic prognostic factors in patients receiving NACT. [12]

Despite the presence of an immune response, tumors continue to grow, a process that has been referred to as “immune escape.” Tumor cell escape can occur through multiple different mechanisms. [14] Tumor cells themselves promote an immunosuppressive microenvironment by producing suppressive cytokines including TGF-β, VEGF, or indoleamine 2,3-dioxygenase. The tumor microenvironment also contains immune cells such as regulatory T cells and myeloid-derived suppressor cells that function to suppress the immune response. At the individual tumor cell level, alterations leading to decreased immune recognition (such as loss of tumor antigens, downregulation of major histocompatibility complex molecules, or loss of antigen processing function within the tumor cell), or increased resistance to the cytotoxic effects of immunity (such as via induction of anti-apoptotic mechanisms) can promote tumor

growth. Finally, tumor cells can upregulate T cell-inhibitory molecules such as programmed death ligand 1 (PD-L1), one of two known ligands for programmed death-1 (PD-1), a T cell inhibitory molecule.

Activating the immune system for therapeutic benefit in cancer is an area of active investigation. Multiple forms of immunotherapy have been described including vaccines targeting tumor antigens, adoptive T cell therapy, and monoclonal antibodies targeting T cell-inhibitory molecules including PD-1 (or it's ligand PD-L1) or the related cytotoxic T-lymphocyte associated protein 4 (CTLA-4). Clinical trials of ipilimumab, a mAb targeting CTLA-4, in patients with metastatic melanoma showed improvements in OS leading to FDA approval for this indication. [15] In September 2014, the anti-PD-1 antibody pembrolizumb was the first agent targeting the PD-1/PD-L1 interaction to receive FDA approval. Pembrolizumab is approved for use in patients with advanced or unresected melanoma not responding to other therapies. Several trials evaluating other mAbs targeting PD-1 and PD-L1 have shown promise in other tumor types including non-small cell lung cancer and renal cell carcinoma. [16] There is data suggesting that PD-L1 expression on the tumor may be a biomarker predicting response to this class of therapy. [16] In a study recently published by our group, we showed PD-L1 expression in 20% of TNBC tumors suggesting that targeting PD-1 or PD-L1 may have therapeutic benefit in TNBC. [17] Ongoing studies are evaluating these agents in patients with metastatic TNBC. Included among these is a phase I trial being conducted by Genentech evaluating their anti-PD-L1 antibody MPDL2380A in combination with nab-paclitaxel.

3.1.6 Clinical Response with Immunotherapies

Evaluating response to immunologic agents in patients with solid tumors has been challenging. Previous evaluations such as the RECIST criteria have looked to pure percentages of growth as a means of response or progression. This has been demonstrated to be challenging in patients who are receiving immunotherapies. Although some reported results have shown tumor regression, others have shown delayed response or even growth of the tumor prior to long term regression. The growth of the tumor in several cases of patients who have had solid tumors, received immunologic agents and then eventually had significant responses had early increase in size of the tumor felt to be consistent with T cell or immunologic infiltration of the tumor.[18-20]

Given this observation, the immune related Response Criteria (irRC) criteria was developed[18]:

Tumor Burden = the sum of perpendicular diameters (SPD) of the index lesion + SPD of any new measurable lesions.

A patient has been considered to be progressing if the tumor burden as defined above does not increase by 25% as compared with the baseline at 2 consecutive time points at least 4 weeks apart.

With regards specifically in metastatic triple negative breast cancer, 2 studies were presented at the 2014 San Antonio Breast Cancer Symposium. Nanda et al. presented a Phase I study of MK-3475 which is a PD-1 inhibitor in metastatic triple negative breast cancer patients. Thirty-two women were treated after multiple previous lines of therapy. Five of the patients had a partial response and have continued on therapy with a durable response >40 weeks. One of the patients had initial progression and then continued with stable disease.[21] At the same meeting, Emens et al. presented 12 patients treated with atezolizumab and two patients had a new lesion identified and then went onto have significant tumor response.[22]

To our knowledge this will be the first instance of evaluating this response in the neoadjuvant setting.

3.2 Atezolizumab

3.2.1 Background: Atezolizumab

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

3.2.2 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were, thus, undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients. Refer to the atezolizumab Investigator's Brochure for details on the nonclinical studies.

3.2.3 Clinical Experience with Atezolizumab

3.2.3.1 Ongoing Clinical Studies

Current studies of atezolizumab include one ongoing Phase Ia monotherapy study, three ongoing combination studies, five Phase II studies, and one Phase III study. Details of all ongoing studies can be found in the atezolizumab Investigator's Brochure.

Phase Ia Study PCD4989g

Study PCD4989g is a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary

evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks to patients with locally advanced or metastatic solid malignancies or hematologic malignancies. Ongoing expansion cohorts are studying the efficacy in patients with pancreatic cancer, bladder cancer, breast cancer, esophageal cancer, prostate cancer, small-cell lung cancer, malignant lymphoma, multiple myeloma, and other less common tumor types.

This multicenter Phase I study was presented at the San Antonio Breast Cancer Symposium in December, 2014. The published study abstract describes that the study selectively enrolled a cohort of patients with PD-L1-positive metastatic TNBC. PD-L1 positivity was centrally evaluated based on the PD-L1 immunohistochemistry (IHC) status of tumor-infiltrating immune cells (ICs). Eligible patients received atezolizumab 15 or 20 mg/kg IV every 3 weeks for up to 1 year. The objective response rate (ORR) was assessed by RECIST v1.1. Atezolizumab immune correlates were evaluated for tumor and circulating biomarkers.

Twelve patients were treated with atezolizumab and evaluable for safety. All 4 patients (33%) with visceral metastases had liver metastases, and 1 patient (8%) had bone metastases. 92% of patients received ≥ 2 prior therapies. Prior chemotherapies included anthracycline (92%), taxane (75%) and platinum (42%). Grade 3-4 treatment-related adverse events (AEs) occurred in 8% of patients (1 event of Grade 3 adrenal insufficiency). One patient had an immune-related AE (Grade 2 pyrexia). No treatment-related deaths were observed. Nine patients were dosed by November 16, 2013 and evaluable for efficacy. The ORR was 33%, including 1 CR and 2 PRs. Responders included patients with visceral metastases at baseline. At the time of the clinical data cut-off, all responses occurred within 6 weeks of the first dosing of atezolizumab, and all of the responses were ongoing. The median duration of response had not been reached. One patient achieved stable disease as best response. Two additional patients had tumor shrinkage (-43% and -44% change in target lesions, respectively) but were not counted as RECIST responders due to the appearance of new lesions, which is likely attributable to pseudo-progression. In conclusion atezolizumab treatment was well tolerated and was associated with objective clinical activity in patients with pretreated metastatic TNBC.

Phase Ib Study GP28328

Ongoing Phase Ib Study GP28328 is evaluating the safety and pharmacology of atezolizumab administered with bevacizumab alone (Arm A) or with bevacizumab plus leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX; Arm B) in patients with advanced solid tumors. Additional cohorts have been included to investigate atezolizumab in combination with carboplatin plus paclitaxel, in combination with carboplatin plus pemetrexed, in combination with nab-paclitaxel in patients with advanced TNBC, and in combination with carboplatin plus nab paclitaxel, pemetrexed, and cisplatin in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

As of 10 May 2014, 90 patients had been enrolled in this study: A total of 88 of 90 patients (97.8%) reported at least one adverse event while on study drug. The majority of these were Grade 1 and 2 in severity. The five most commonly reported adverse events included fatigue, nausea, diarrhea, decreased appetite and pyrexia. However, none of the toxicities were felt to be additive to the chemotherapy toxicity.

Therefore this agent has shown to have activity in patients with resistant TNBC in addition to an acceptable safety profile when given in combination with nab-paclitaxel, which would be considered a standard therapy after anthracycline-based chemotherapy for early stage breast cancer.

Phase Ib Study GP28384

Ongoing Phase Ib Study GP28384 is evaluating the safety and pharmacology of atezolizumab administered in combination with vemurafenib in patients with previously untreated BRAF V600-mutation–positive metastatic melanoma.

Phase Ib Study GP28363

Ongoing Phase Ib Study GP28363 is evaluating the safety and pharmacology of atezolizumab administered in combination with cobimetinib (MEK inhibitor) in locally advanced or metastatic solid tumors.

Phase II Study GO28625 (FIR)

Ongoing, single-arm, Phase II Study GO28625 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. In particular, this study is evaluating whether archival or fresh tumor tissue is more predictive of response to atezolizumab. Safety and efficacy data are not yet available for this study.

Phase II Study GO28753 (POPLAR)

Study GO28753 is a randomized, open-label, Phase II study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28753 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is overall survival (OS) for both the PD-L1–positive population and the overall study population.

Phase II Study GO28754 (BIRCH)

Ongoing, single-arm, Phase II Study GO28754 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. Safety and efficacy data are not yet available for this study.

Phase II Study WO29074

Ongoing Phase II Study WO29074 is evaluating the safety and efficacy of atezolizumab monotherapy or the combination of atezolizumab and bevacizumab versus sunitinib in treatment-naïve patients with renal cell carcinoma (RCC). Safety and efficacy data are not yet available for this study.

Phase II Study GO29293

Ongoing Study GO29293 is a single-arm, open label, Phase II study to assess the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic UBC. The co-primary endpoints of this study are independent review facility (IRF)-assessed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and investigator-assessed ORR according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Phase III Study GO28915 (OAK)

Study GO28915 is a randomized, open-label, Phase III study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28915 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is OS for both the PD-L1–positive population and the overall study population.

3.2.3.2 Clinical Safety

The presented safety data for atezolizumab have been derived mainly from the treatment of patients in Phase Ia Study PCD4989g. As of 11 May 2015, there were 558 safety evaluable patients from the Phase Ia Study PCD4989g. The median duration of treatment was 12.14 weeks (range: 0.0-71.4 weeks), and the median number of atezolizumab cycles administered was 5.0 (range: 1−19 cycles). Currently, no maximum tolerated dose, no dose-limiting toxicities and no clear dose-related trends in the incidence of adverse events have been determined.

Adverse Events (AEs)

In all 558 treated patients in Study PCD4989g, 520 (93%) patients experienced an adverse event regardless of attribution to atezolizumab. Treatment-related adverse events (per investigator's assessment of causality) were reported in 376 patients (67.4%). The majority of these AEs were Grade 1 or 2 in maximum severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

The most frequently observed adverse events (≥10% of patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

Grade 3-4 adverse events were reported in 239 patients (42.8%) of which 66 (11.8%) were considered related by the investigator. Grade 3 and 4 AEs considered related included dyspnea, pneumonitis, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyltransferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia. Safety findings in the TNBC cohort of study PCD4989g are consistent with the data observed in the overall study population.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding clinical safety.

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding immune mediated AEs and identified risks (Adverse Drug Reactions) observed in patients treated with atezolizumab.

Preliminary Clinical Safety in Combination with Platinum-Based Doublet Chemotherapy: Phase 1b Study GP28328

Study GP28328 is a trial of the safety and pharmacology of atezolizumab administered with bevacizumab and/or chemotherapy in patients with advanced solid tumors. Arm A evaluates 1200 mg

atezolizumab + bevacizumab administered q3w in patients with multiple solid tumor types, including separate expansion cohorts in colorectal cancer (CRC) and renal cell carcinoma (RCC). Arm B evaluates atezolizumab + bevacizumab and FOLFOX administered q2w in patients with multiple solid tumor types, including colorectal cancer and breast cancer. Arms C, D, and E evaluate atezolizumab administered q3w in chemotherapy-naïve non-small cell lung cancer (NSCLC) patients in combination with carboplatin + paclitaxel, carboplatin + pemetrexed, and carboplatin + nab-paclitaxel, respectively. As of 10 May 2014, preliminary safety data are available from 90 treated patients. Of these patients, 88 (98%) reported one or more AEs. The five most commonly reported AEs included fatigue, nausea, diarrhea, decreased appetite and pyrexia. Immune mediated events were infrequently reported. The following were observed in the overall population: rash (11.1%), ALT increased (5.6%), AST increased (5.6%) and hypothyroidism (1.1%).

No additive adverse effects were observed when atezolizumab was administered in combination with either bevacizumab or nab-paclitaxel chemotherapy.

3.2.4 Clinical Activity

Anti-tumor activity, including RECIST-based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types, including NSCLC, RCC, melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma treated with atezolizumab monotherapy in Study PCD4989g. Among 386 evaluable patients enrolled prior to 1 July 2013 (data cutoff of 1 January 2014), there were 47 patients with responses with a median duration of response of 75.7 weeks (range: 11.7+ to 85.9+ weeks, where "+" denotes censored value). The majority of these responses have been durable, with 72.3% (34/47) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to atezolizumab.

3.2.4.1 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution at steady state (Vss) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and AEs or infusion reactions has been observed.

3.2.4.2 Rationale for atezolizumab Dosage

Currently available PK and ATA data from Study PCD4989g suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both

maintain trough concentration (C_{trough}) ≥ 6 μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab A relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected when atezolizumab is administered q3w (equivalent to an average body weight–based dose of 15 mg/kg).

3.2.5 Nab-paclitaxel and Combination Treatment with atezolizumab

Preliminary safety data from study GP28328 indicate that atezolizumab can be safely combined with chemotherapy (several combinations have been evaluated and determined to be well tolerated; refer to the Atezolizumab Investigator's Brochure for details). Specifically, atezolizumab was tested in combination with carboplatin + Nab-paclitaxel in patients with previously untreated NSCLC; refer to the Atezolizumab Investigator's Brochure for details. No exacerbation of chemotherapy-associated adverse events was reported.

Adverse events commonly reported in 2 or more patients in Arm F (atezolizumab in combination with nab-paclitaxel) included dermatitis, upper respiratory infection, alopecia, peripheral sensory neuropathy, fever, constipation, neutrophil count decreased, anemia, diarrhea, headache, nausea and fatigue.

There is increasing evidence that in addition to causing tumor cell death, certain conventional chemotherapies may have immunogenic effects.[18] Clinical evidence exists to suggest that T-cell and natural killer (NK)-cell functions are enhanced in patients with breast cancer (stage II/III) treated with taxanes, as compared to patients who did not receive taxanes.[19] In addition tumor cell killing by cytotoxic chemotherapy can be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared to standard chemotherapy alone.

Refer to the atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

3.3 Rationale

3.3.1 Rationale for the Study and Selected Subject Population

As previously discussed, approximately 50% of patients with TNBC treated with standard taxane and anthracycline-based neoadjuvant chemotherapy (NACT) will have either pCR (RCB-0) or minimal RD (RCB-I) at the time of surgical resection. Those patients have identical and exceptionally good long-term prognosis with a less than 10% risk of developing distant metastatic disease within 5 years. Unfortunately, those with more extensive RD (RCB II-III) have a much worse prognosis, with greater than 50% of patients developing distant metastatic disease within 5 years of initial diagnosis. Additionally, clinical trials of NACT in breast cancer have demonstrated that patients without a response to their first NACT regimen have a very low chance (5%) of achieving pCR after their second NACT regimen. Evaluating the rate of pCR and RCB-I responses in patients treated with atezolizumab in combination with nab-paclitaxel in the neoadjuvant setting is therefore a clinically meaningful endpoint.

Studies have shown that an immune infiltrate has both prognostic and predictive significance in TNBC patients. However, despite the presence of TIL, this immune response is not able to cure TNBC. A promising approach to augmenting antitumor immunity is blockade of T cell inhibitory molecules such as CTLA-4 or PD-1. In a study recently published by our group, we showed PD-L1, one of the known ligands for PD-1, to be expressed in 20% of TNBC tumors. [9] This suggests that targeting PD-1 or PD-L1 may have therapeutic efficacy in TNBC.

Treatment with chemotherapy results in tumor cell death which may result in the release of antigens and generation of an immune response against these antigens. It is possible that the generated immune response could be augmented by treatment with atezolizumab and that persistence of this immune response could lead to improvements in longer term outcomes, thus justifying evaluating the impact of atezolizumab in combination with nab-paclitaxel on DFS, one of the trial's secondary endpoints. Another secondary endpoint is to confirm the safety of the combination of atezolizumab with nab-paclitaxel. This combination has been shown to be safe in a small population of patients with metastatic TNBC however safety must be confirmed in patients with earlier stage, potentially curable disease being treated in the neoadjuvant setting.

Published data from other studies evaluating antibodies targeting the PD-1/PD-L1 interaction have suggested that PD-L1 expression may be a biomarker predicting response to treatment.[20] These data are from a small subset of 42 patients enrolled on a phase I trial evaluating the anti-PD-1 antibody nivolumab. An objective response was seen in 9 of 25 patients whose tumors stained positive for PD-L1 but in none of 17 patients whose tumors were negative. Additional studies are required to further investigate PD-L1 expression as a biomarker as well as to identify other biomarkers that may predict response to immune checkpoint inhibitors thus providing rationale for the proposed exploratory objective for this study.

Nab-paclitaxel has been tested in the neoadjuvant setting at 100 mg/m2 IV weekly x 12 weeks and found to be safe and tolerable.[21] As this is the preferred dosing of nab-paclitaxel in the neoadjuvant setting, this is the dosing regimen chosen for this study.

Taken together, these data provide the rationale for the proposed clinical trial evaluating atezolizumab in combination with nab-paclitaxel, in the neoadjuvant setting to TNBC patients who have failed to respond to anthracycline-based chemotherapy. We hypothesize that this combination will lead to increased response rates which have been shown to predict for improved survival outcomes.

3.3.2 Rationale for Dose Selection/Regimen/Modification

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) and q3w schedule was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g.

Patients will be dosed with a standard dosing regimen of nab-paclitaxel (100 mg/m^2) weekly x 12 weeks for the first part of this study, before surgery.[22] This weekly regimen of nab-paclitaxel was established in a Phase 2 study conducted in patients with previously untreated metastatic breast cancer.

4.0 PATIENT ELIGIBILTY

4.1 Inclusion Criteria

In order to be eligible for participation in this study, the subject must have:

1) Signed written informed consent

2) Histologically confirmed primary invasive adenocarcinoma of the breast with the size of the primary tumor being at least 1.5 cm, or at least 1 biopsy confirmed involved lymph node >1.5 cm, on imaging by either mammography, ultrasound or breast MRI.

3) ER and PR expression both <10% by immunohistochemistry (IHC) and HER2 negative or non-amplified as determined by the current ASCO-CAP criteria which are as follows: HER2 testing by IHC as 0 or 1+. If HER2 is 2+, ISH (in situ hybridization) must be performed. HER2 is positive for gene amplification if:

   - IHC 3+ based on circumferential membrane staining that is complete, intense
   - ISH positive based on:
     Single-probe average HER2 copy number ≥6.0 signals/cell.
     Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2 copy number ≥4.0 signals/cell
     Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2 copy number <4.0 signals/cell
     Dual-probe HER2/CEP17 ratio < 2.0;c,e with an average HER2 copy number ≥6.0 signals/cell

4) No prior treatment for primary invasive adenocarcinoma of the breast such as irradiation, chemotherapy, hormonal therapy, immunotherapy, investigational therapy or surgery other than the anthracycline and cyclophosphamide chemotherapy with or without 5-fluorouracil. Treatment for ductal carcinoma in situ is allowed, such as surgery, hormonal therapy and radiotherapy.

5) ECOG performance status of 0-1.

6) Baseline MUGA or echocardiogram scans with LVEF of > 50%.

7) Patient must have adequate organ function as determined by the following laboratory values:
   - ANC $\geq$ 1500 cells/μL
   - WBC counts $>$ 2500/μL
   - Lymphocyte count $\geq$ 300/μL
   - Platelet count $\geq$ 100,000/μL;
   - Hemoglobin $\geq$ 9.0 g/dL
   - Total bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN) with the following exception: Patients with known Gilbert disease who have serum bilirubin level $\leq$ 3 $\times$ ULN may be enrolled.
   - AST and ALT $\leq$ 3.0 $\times$ ULN

- Alkaline phosphatase ≤ 2.5 × ULN
- Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

  $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
- INR and aPTT ≤ 1.5 × ULN

  This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low-molecular-weight heparin or warfarin) should be on a stable dose.

8) Men or women 18 years of age or older.

9) Women of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 6 months after the last dose of investigational product in such a manner that the risk of pregnancy is minimized. Men on study and for at least 6 months after the last dose of nab-paclitaxel also must be using contraception. Women of childbearing potential (WOCBP) are women who have not been postmenopausal greater than 1 year or undergone a hysterectomy and/or bilateral oophorectomy.

10) Negative serum or urine pregnancy test for women within 72 hours of receiving the first dose of the study medication for women of childbearing potential.

11) Classified as having insufficient tumor shrinkage by imaging (<80% shrinkage after 4 cycles of anthracycline-based chemotherapy based upon diagnostic imaging.

4.2 Exclusion Criteria

1) Women who are pregnant or breast-feeding.

2) Known metastatic disease

3) Disease free of prior malignancy for < 5 years with the exception of curatively treated basal cell carcinoma of the skin, carcinoma in situ of the cervix, or transitional cell carcinoma.

4) Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

5) Has had major surgery within 21 days before Cycle 1, Day 1

6) Uncontrolled inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)

7) Myocardial infarction within 6 months before starting therapy, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or unstable cardiac arrhythmia requiring medication

8) Serious intercurrent infections or non-malignant medical illness that are uncontrolled or the control of which may be jeopardized by this therapy.

9) Psychiatric disorders or other conditions rendering the subject incapable of complying with the requirements of the protocols.

10) History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
    - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
    - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
    - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

        Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

        Rash must cover less than 10% of body surface area (BSA)

        Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

        No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

    (See Appendix F for a more comprehensive list of autoimmune diseases)

11) Known to be human immunodeficiency virus positive

12) Patients with prior allogeneic stem cell or solid organ transplantation

13) History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

14) Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B

core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

15) Active tuberculosis

16) Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study.

    Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

17) Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug, whichever is shorter, from Cycle 1 Day 1.

18) Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 1 week prior to Cycle 1 Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., dexamethasone prior to the anthracycline-based chemotherapy for nausea) may be enrolled in the study.

    The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

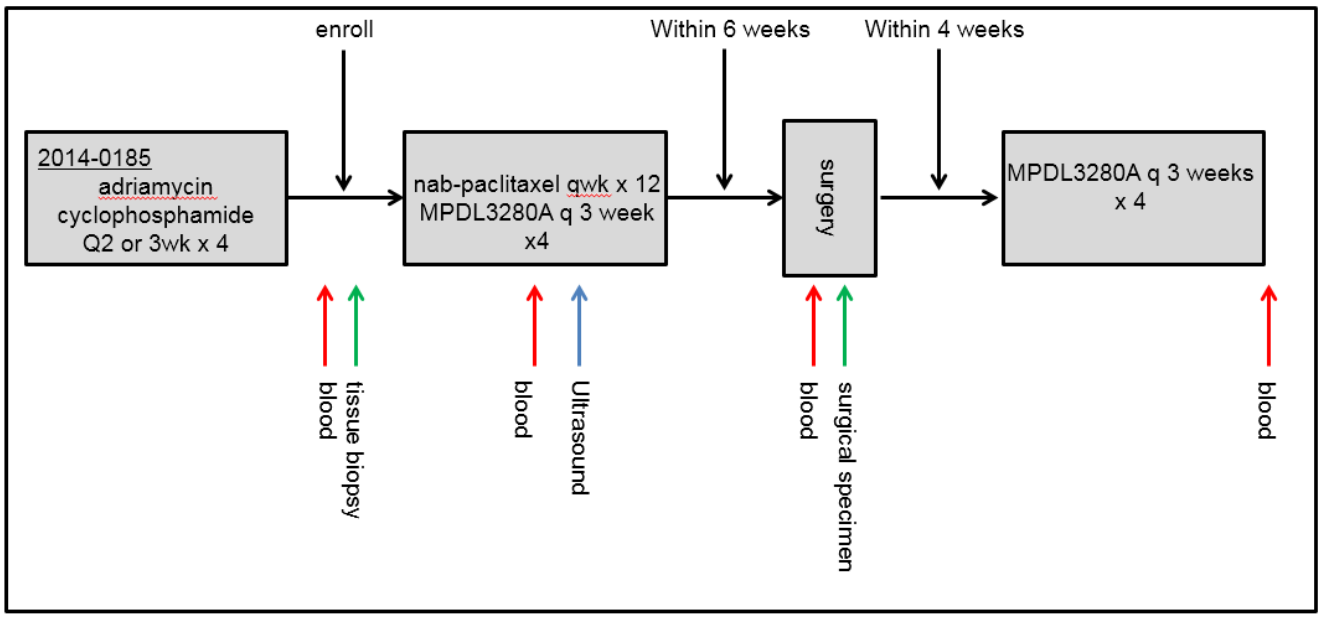
19) Concurrent disease or condition that would interfere with study participation or safety, such as any of the following:

    - Active, clinically significant infection either grade > 2 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or requiring the use of parenteral anti-microbial agents within 14 days before Day 1 of study drug
    - Clinically significant bleeding diathesis or coagulopathy, including known platelet function disorders
    - Non-healing wound, ulcer, or bone fracture

20) Known hypersensitivity to any of the components of atezolizumab or nab-paclitaxel

21) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

5.0 TREATMENT PLAN



NOTE: MPDL3280=Atezolizumab

5.1 Study Design

In this study, we intend to assess the ability of the addition of atezolizumab to nab-paclitaxel administered in the neoadjuvant setting to increase response rates in patients with TNBC that are identified as non-responders to standard chemotherapy.

Patients may be identified as part of the MD Anderson triaging protocol as previously described. Patients will be administered atezolizumab in combination with nab-paclitaxel after which they will undergo surgery. Following surgery, patients will continue on atezolizumab for an additional 3 months to complete 6 months total of atezolizumab therapy.

The trial will allow us to test the hypothesis that among patients with TNBC who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, the combination of atezolizumab and nab-paclitaxel administered in the neoadjuvant setting will increase pCR rates. The trial's primary endpoint is to evaluate the pCR and RCB-I rates in patients treated with atezolizumab in combination with nab-paclitaxel with a secondary endpoint of determining 3 year DFS.

Atezolizumab will be administered at 1200mg IV every 3 weeks (q3w x 4 doses) for 12 weeks in the neoadjuvant setting in combination with nab-paclitaxel (100 mg/m2 IV weekly for 12 weeks).

Within 4 weeks after surgery, patients will start another 4 cycles of atezolizumab (1200mg IV q3w) in the adjuvant setting to complete a total of 8 cycles of treatment with MPDL3280A.

Thirty-seven patients will be enrolled in this study.

Due to scheduling, study visits may occur +/- 3 days from the required time point. It may be necessary to perform assessments at unscheduled time points if deemed clinically necessary by the investigator.

All patients will undergo definitive breast surgery after four cycles (12 weeks) of atezolizumab + nab-paclitaxel study treatment. Surgery will be expected within 6 weeks of the completion of neoadjuvant chemotherapy. Tumors must be removed by either lumpectomy or mastectomy with clinically appropriate axillary surgery. The surgical specimens (breast and axillary lymph node tissue) will be evaluated for pathological response (defined per protocol) by breast-specific pathologists at the MD Anderson Cancer Center.

Tissue analysis will be performed on biologic specimens from patients enrolled on the phase II portion of the parent study and receiving the combination of atezolizumab with nab-paclitaxel in the neoadjuvant setting. Biopsies prior to and at the end of the anthracycline portion of the parent clinical trial are already being collected as part of the parent protocol 2014-0185. Ideally up to 4 additional core biopsies (passes) will be collected at the same time point for the purposes of this trial (2014-1043), provided enough material is available.

A portion of the surgical specimen at the time of the definitive surgery will be collected for further correlative studies. Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation by scheduled ultrasound. Ultrasounds will be done prior to initiation of therapy and at 6 weeks while on study therapy +/- 1 week as standard of care.

If there is increase in size of the mass on ultrasound as defined by:

The sum of perpendicular diameters of the index lesion in addition to the sum of the perpendicular diameters of a new lesion when compared to the baseline measurement at the entry onto this study as measured at 2 separate time points at least 4 weeks apart, the patient will come off study and move forward with surgery.

If there is growth, but less than 25% as defined above, then a second ultrasound will be ordered at 4 weeks +/- 3 days to evaluate for progression. If Progression at that time is identified, the patient will go to surgery, however the study medication will continue as defined in the protocol after surgery.

The treating physician can order ultrasounds sooner at their discretion if there are concerns of progression of disease.

Should growth be observed on the breast ultrasound performed per standard of care after about 6 weeks of study therapy, a biopsy can be performed. If the disease is shown to have increased immune infiltrate the patient can continue on therapy.

If a new site of disease or lymph node is identified and confirmed by biopsy to be a new sight of carcinoma and not immune-infiltrate, that patient would be considered to have progression of disease and the patient would discontinue study treatment.

Therapy will be discontinued should the treating physician determine that the response is consistent with progression of disease.

Laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (aPTT and INR)
- Pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) x 1 as part of the screening process for eligibility of this study.
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (TSH, free T3, and free T4),
- Epstein-Barr virus (EBV) serology (EBNA IgG), Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated
  - HBV DNA test is required for patients who have known positive serology for anti-HBc
  - HCV RNA test is required for patients who have known positive serology for anti-HCV

  Please see study calendar in Section 8.0 for full details of scheduling of laboratory assessments.

5.2 Concurrent and Supportive Care

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g., antiemetics, colony stimulating factors), with the following exceptions:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients.

Research Electronic Data Capture (REDCap) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies including herbal supplements.

5.2.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as

per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix H).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 5.2) should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

5.2.2 Excluded Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited in the neoadjuvant setting. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 5.2)

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity
- The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) should only be done for rescue from clinically significant neutropenia and not routinely dosed between nab-paclitaxel weekly dosing, instead nab-paclitaxel should be delayed and dose reduced as discussed in section 6.2.2

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may

attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

Any patient anticipated to receive administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study is excluded

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

5.3 Duration of Study

The study is expected to complete accrual within 2 years from study initiation. The duration of chemotherapy treatment per subject will be approximately 6 months on atezolizumab + nab-paclitaxel (3 months in the neoadjuvant setting) followed by 3 months of atezolizumab in the adjuvant setting. As part of the parent protocol, patients will be followed for survival endpoints for 3 years.

5.4 Progression While on Study

Subjects who progress while on atezolizumab + nab-paclitaxel will automatically be considered non-responders to atezolizumab + nab-paclitaxel and will proceed to the standard of care therapy of the treating physician's choice or proceed to surgery if the treating physician feels that that is in the patient's best interest. Progression will be defined as a greater than 25% of the sum of perpendicular diameters of the index lesion in addition to the sum of the perpendicular diameters of a new lesion when compared to the baseline measurement at the entry onto this study as measured at 2 separate time points at least 4 weeks apart.

5.5 Subject Withdrawal/Discontinuation Criteria

5.6 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Patient non-compliance
- Pregnancy

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in REDCap.

However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study prior to surgery will be replaced.

5.7 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Toxicity that jeopardizes the patient's safety in the opinion of the treating physician and/or principle investigator
- Progression of disease

The primary reason for study treatment discontinuation should be documented in REDCap. Patients who discontinue study treatment prior to surgery will be replaced.

5.8 Study and Site Discontinuation

The Supporter has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.

The Supporter will notify the investigator if the Supporter decides to discontinue the study.

The Supporter has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

<u>Removal from study</u>

Data will be collected until 3 years post the final cycle of study treatment is completed as part of their participation in the parent trial. The patient will then come off study with regards to data collection.

Should a patient withdraw consent, then the patient will be removed from study at that time and no further data will be collected.

6.0 EXPECTED TOXICITIES AND DOSING DELAYS/MODIFICATIONS

6.1 General Plan to Manage Safety Concerns

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring.

Eligibility Criteria
Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account.

Monitoring
Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the study calendar. If a dose is held due to toxicity, a patient may resume treatment from the treatment cycle that was held, once the toxicity has resolved and/or as clinically indicated. Patients will be followed for safety for 30 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see study calendar for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest (see Section 10.4.2.11) will be recorded including those considered unrelated or expected). In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

6.1.1 Administration of first and subsequent infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication is administered • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse (one vial in 250 mL NaCl) over 60 (± 15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (± 5-minute windows are allowed for all timepoints), and if clinically indicated. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 (± 10) minutes after the infusion, and if clinically indicated. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (± 10) minutes. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (± 15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 (± 10) minutes after the infusion, and if clinically indicated. If no reaction occurs, continue subsequent infusions over 30 (± 10) minutes with same schedule for recording vital signs.

6.1.2 Management of Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The primary approach to Grade 1-2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune mediated adverse events, atezolizumab should be held and oral/parenteral steroids administered. Recurrent Grade 2 immune mediated adverse events may also mandate holding atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune mediated adverse events.

See the Atezolizumab Investigator's Brochure for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events.

6.1.3 Nab-Paclitaxel Dose Modification and Management of Specific Adverse Events

Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy should have their nab-paclitaxel dosage reduced to 75 mg/m^2 for subsequent cycles. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 50 mg/m^2. For Grade 3 sensory neuropathy, hold treatment until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent cycles.

If Grade 3 hepatic toxicity occurs at any time, the nab-paclitaxel dose should be permanently reduced to 75% of the starting dose (i.e., to 75 mg/m^2). Nab-paclitaxel will be permanently discontinued for Grade 4 hepatic toxicity.

If nab-paclitaxel is withheld, hepatic values must recover to Grade </= 1 within 3 weeks or nab-paclitaxel treatment will be discontinued.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement.

6.2 Nab—PACLITAXEL DOSING

6.2.1 Dosing

Nab-paclitaxel will be dosed at 100 mg/m2 IV weekly x 12 weeks. Known side effects of nab-paclitaxel identified in the MDACC research database last updated 4/22/14 include:

Nab-paclitaxel Side Effects

Common (occurring in more than 20% of patients)

abnormal EKG	low blood cell counts (red, white, platelets)	nerve damage (loss of sensory function)
hair loss (partial or total)	abnormal liver test (possible liver damage)	weakness
nausea		pain (muscle, joint)
diarrhea		infection

Occasional (occurring in 3-20% of patients)

swelling

low blood pressure (possible dizziness/fainting)

high blood pressure

chest pain

sudden stopping of the heart

fast heartbeat

blood clots in a vein (possible pain, swelling, and/or redness)

vomiting

mouth blisters/sores

abnormal liver tests (possible yellowing of the skin and/or eyes)

nerve damage (possible numbness, pain, and/or loss of motor function)

vision problems

abnormal kidney test (possible kidney damage)

difficulty breathing

blood clots in the lung (possible failure to breathe)

cough

allergic reaction (possible chest pain, difficulty breathing, flushing, and/or low blood pressure)

Rare but serious (occurring in fewer than 3% of patients

irregular/slow heartbeat

decreased blood supply to the heart

heart attack

heart failure

severe heart problems

stroke and/or temporary stroke symptoms

fever

hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)

severe sunburn-like rash at site of previous radiation (called radiation recall)

inflammation of the pancreas (possible abdominal pain)

hole in the intestines (possibly leaking contents into the abdomen)

dehydration

intestinal blockage

paralysis of the intestines

blurred vision

damage to an eye nerve

collapsed lung (possible difficulty breathing)

swelling under the central part of the eye (vision loss)

nerve damage (affecting movement)	decreased blood flow to part of the bowel (possibly causing death of tissue)	lung inflammation (possible difficulty breathing)
very severe blistering skin disease (with ulcers of the skin and digestive tract)		lung damage at the site of prior radiation
very severe blistering skin disease (loss of large portion of skin)		

The following side effects were reported with a similar drug (paclitaxel) and may also be caused by nab-paclitaxel:

decreased brain function due to liver damage	liver damage and/or failure	tissue death at the injection site caused by drug leakage
inflammation at the site of previous tissue death	lung damage (possible difficulty breathing)	

6.2.2 Nab-paclitaxel dose reductions

Patients may proceed with nab-paclitaxel dosage for ANC >/= 1000 /mm3, platelets >75, Hemoglobin >8.0.

Dosing of nab-paclitaxel should be held for 1 week and dosing can resume once levels reach the above specifications with a dose-reduction and/or granulocyte-stimulating factor in the subsequent cycles are allowed at the Investigator's discretion.

Should the patient experience dose-limiting toxicities from the nab-paclitaxel felt to require a dose-reduction of nab-paclitaxel by the treating physician and/or per specifications in the package insert for nab-paclitaxel, should be dose reduced to:

Level 0= 100 mg/m2

Level -1 = 90 mg/m2

Level -2 = 80 mg/m2

Level -3 = 70 mg/m2

If further dose reductions are required after a level of -3 despite growth factor support, patient should be discontinued from the nab-paclitaxel and per investigator discretion can continue with the investigational intervention, surgery and the post-surgery scheduled infusions.

Patients who experience severe neutropenia or severe sensory neuropathy should have their nab-paclitaxel dosage reduced to 75 mg/m2 for subsequent cycles as detailed in section 6.1.3. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 50 mg/m2. For Grade 3 sensory neuropathy, hold treatment until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent cycles.

For dose reductions based on hepatic toxicity see Section 6.1.3.

Patients experiencing > grade 2 non-hematologic drug toxicity that is unresponsive to symptomatic support may undergo dose reduction of the responsible drug(s) as indicated. Other drugs within the regimen can be continued at full dose per the treating physician's discretion.

6.2.3 Study Drug: Atezolizumab

Once marketing authorization is received commercial atezolizumab will be used and will not be provided by Genentech for “on-label” studies. For studies done before marketing authorization and/or "out of label", atezolizumab will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any atezolizumab drug that is not reimbursed. For studies done “out of label,” atezolizumab will be provided free of charge by Genentech. The Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.

6.2.3.1 Formulation

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C – 8°C (36°F – 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the atezolizumab Investigator’s Brochure.

6.2.3.2 Dosage, Administration, and Storage

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [± 2] days). atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient’s vital signs (heart rate, respiratory rate, blood

pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For further details on the storage and preparation of atezolizumab, see the Pharmacy Manual and the Investigator's Brochure.

7.0 CORRELATIVE STUDIES

Tumor tissue and peripheral blood will be collected prior to beginning therapy with atezolizumab and nab-paclitaxel and at selected timepoints on treatment as well as at the time of surgery. Residual sample material available after completion of the designated analyses may be used in the future for identification of additional predictive biomarkers or to enhance understanding of disease biology. If biomarker samples are drawn but study drug(s) is not administered, samples will be retained. A description of each assay system is described below.

7.1 Tissue

Tissue samples will be obtained prior to beginning atezolizumab and nab-paclitaxel (core biopsies) and at the time of surgical resection. Prior to beginning atezolizumab and nab-paclitaxel, at least two core biopsies will be obtained; one to be processed fresh to assess for TIL by flow cytometry, and the second to be formalin fixed paraffin embedded (FFPE) for assessment of the immune cell infiltrate and PD-L1 expression by immunohistochemistry and immunofluorescence. At the time of surgical excision, the attending breast pathologist presenting in the pathology lab to gross the resected specimen will determine if there is enough residual tumor available to provide a fresh specimen for TIL analysis. FFPE slides from the resected surgical specimen will also be obtained.

If available up to 10 tissue slides from any one of the research biopsies or surgical sample will be sent to Genentech for the following assessments:

- Assessment of PDL1 tumor protein expression
- Evaluation of intratumoral CD8+ T cells as potential favorable prognostic factor in TNBC
- Analysis of tumor-derived RNA expression (Fluidigm or Nanostring)

7.1.1 Characterization of TIL – Fresh tumor specimens

Fresh tumor tissues will be used to generate a single cell suspension to evaluate the immune cell infiltrate and expression of T cell co-stimulatory/inhibitory molecules by flow cytometry. The following antibodies will be used: aqua live/dead, CD3, CD4, CD8, CD25, and CD127 to identify effector and regulatory T cells. CD45, CD11c, CD14 and CD335 will be used to identify myeloid cells, dendritic cells, monocytes and natural killer cells respectively. Antibodies to evaluate T-cell co-stimulatory/inhibitory molecules will include but may not be limited to OX-40, GITR, 4-1BB, ICOS, PD-1 and CTLA-4.

7.1.2 Characterization of TIL–Formalin-fixed, paraffin-embedded (FFPE) specimens.

A recent report on predictive correlates of response to the atezolizumab antibody in cancer patients showed that patients with tumors expressing PD-L1 in tumor infiltrating immune cells were more likely to respond to therapy.[23] This correlative work was performed on tumors obtained from patients with non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck squamous cell carcinoma, gastric cancer, colorectal cancer and pancreatic cancer although preliminary work presented at the 2014 San Antonio Breast Cancer symposium demonstrated similar results). PD-L1 expression in pre- and post-treatment specimens will be determined by immunohistochemistry using an anti-PD-L1 antibody.

To evaluate for co-localization of PD-L1 and select tumor-infiltrating immune cells, multispectral, multiplexed immunofluorescence will be performed using tyramide signal amplification (TSA) technology. TSA signal molecules are covalently bound to tyrosine residues in proteins proximal to the target allowing for the resolution and stability required for multiplex assays. The panel includes antibodies against CD3 (T cells), $CD20^{+}$ (B cells), CD163 (macrophages), and CD11c (dendritic cells). In addition, the panel includes an antibody against PD-L1 and an antibody against cytokeratin to differentiate tumor cells. Briefly, slides will be stained with the indicated antibodies after which multispectral imaging will be performed using the Vectra Automated Quantitative Pathology imaging System and the Lamina Multilabel Slide Scanner (Perkin Elmer). InForm image analysis software will be used to quantify the expression of the various immune cells comprising the infiltrate both in the tumor and the surrounding stroma.

7.1.3 Characterization of the tumor-immune microenvironment – Formalin-fixed, paraffin-embedded (FFPE) specimens.

To better understand the immune and molecular features that are most critical in promoting resistance to neoadjuvant therapy, we deconvoluted gene expression data from bulk whole transcriptomic sequencing (RNAseq) of pre-treatment tumor biospecimens from 99 consecutive patients with TNBC receiving neoadjuvant therapy. Interestingly, lower $CD4^{+}$ T-cell infiltration was associated with resistance to neoadjuvant therapy ($p=0.0078$) and there was a trend towards an association between higher macrophage infiltration and resistance to neoadjuvant ($p=0.064$). Of note, the degree of $CD8^{+}$ T-cell infiltration was not associated with resistance to neoadjuvant therapy in this cohort of patients ($p=0.14$). However, through the use of multiplex immunofluorescence, we demonstrated that increased spatial separation of $CD8^{+}$ T-cells from tumor cells was associated with resistance to NAT (median 32 μm [pCR] vs 42 μm [non-pCR]). Collectively, these data suggest that the precise phenotypic composition of TILs along with their degree of interaction with tumor cells may further help predict resistance to NAT in TNBC and inform the development of innovative clinical trials for patients with NAT-resistant TNBC.

Building on our preliminary data demonstrating that the specific phenotype of TILs (RNA-based predictions) and their interactions with tumor cells are a critical determinant of response to NAT in TNBC, we will further characterize the immune cell subpopulations, their activation states, and interactions with tumor cells using the Nanostring GeoMx Digital Spatial Profiler (DSP) in collaboration with the Department of Translational Molecular Pathology at MD Anderson. The Nanostring GeoMx DSP is a cutting edge high-plex protein-based assay which enables simultaneous quantification of up to 96 protein targets with spatial resolution. In close collaboration with the Department of Translational Molecular Pathology, we have put together a list of targets spanning immune cell morphology and activation markers, immune-oncology drug targets, tumor cell survival pathway markers, as well as phosphorylated protein targets for targetable kinases known to influence anti-tumor immunity (PI3K and MAPK pathways). Four μm sections will be stained using Nanostring standard protocol with the following morphology biomarkers: pancytokeratin (CK), CD45, CD3 and Syto13; and the DSP Human Immuno-oncology Protein panels and signaling pathway panels (Modules: Immune Cell Profiling Core, IO Drug Target, Immune Activation Status, Immune Cell Typing, Pan-Tumor, Cell Death, PI3K/AKT Signaling, MAPK Signaling) (88 antibodies). We will select up to 6 regions of interest (ROI) for each

tumor tissue sample containing tumor and immune cells, we will segment each ROI in up to 3 areas of illumination (AOI) representing the different tumor and immune cells, based in the expression of the morphology biomarkers (Malignant cells, CK+; T-cells, CD45+CD3+; and other immune cells, CD45+CD3-). For each run we will use appropriate positive and negative control tissue. Indexing oligos will be released by the Sequential UV light exposure of each AOI, and will be quantified on NanoString's nCounter® system. Heat maps and box plots will be used to visualize protein expression patterns. Promising targets will be validated using chromogenic immunohistochemistry.

7.2 Peripheral blood mononuclear cells (PBMC)

PBMC samples will be collected prior to beginning atezolizumab + nab-paclitaxel, midway through treatment (around week 7), at the time of surgery and at completion of atezolizumab therapy

7.2.1 Immunophenotyping.

To further explore findings from prior trials evaluating atezolizumab, that showed a non-significant increase in activated proliferating CD8+ T cells (CD8+HLA-DR+Ki67+), PBMC will be analyzed by flow cytometry for CD3, CD8, HLA-DR and Ki-67. In addition, the proportion of specific immune cells including lymphocyte subsets as well as expression levels of T cell co-stimulatory/inhibitory markers will be quantified in PBMC. Analyses may include, but not necessarily be limited to, the proportion of T, B and NK cells, granulocytes, the proportion of memory and effector T cell subsets, and expression of levels of PD-1, PD-L1, other B7 family members and ICOS.

7.2.2 T cell repertoire analysis

Lack of diversity of the peripheral T cell compartment has been shown to correlate with poor overall survival in metastatic breast cancer.[24] It has therefore been suggested that a diverse and activated immune environment is better able to eradicate tumor than a skewed repertoire of naïve and tolerized T cells. In order to explore whether a diverse T cell repertoire is predictive of response to therapy, next generation, high-throughput DNA sequencing will be performed on DNA isolated from peripheral blood to quantitate the composition of the T cell repertoire prior to, during and at completion of therapy with atezolizumab and nab-paclitaxel.

7.2.3 Serum

Serum samples will be collected prior to beginning atezolizumab + nab-paclitaxel, midway through treatment (around week 7), at the time of surgery and at completion of atezolizumab therapy. Polyfunctional cytokine responses will be assessed using the Meso Scale Discovery (MSD) platform which has the capability to simultaneously measure multiple analytes from a single sample. A MSD V-plex platform that measures 40 analytes (including but not limited to: IFN-γ, TNF-α, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-15, IL-17, IL-18 and) will be used.

7.2.3.1 Storage of Specimens

All PBMC and serum specimens will either be used immediately to perform the designated assay or will be stored in Dr. Mittendorf's laboratory. PBMC will be stored in liquid nitrogen, serum will be stored at -80º. Fresh tissue samples will be placed in RPMI then processed immediately for TIL analysis by flow cytometry. FFPE blocks will be maintained until time at which assays will be performed. To perform multiplex immunofluorescence staining, tissue sections will be cut at a thickness of 4 microns and placed on positively charged slides. If FFPE tissue availability is an issue, slides for multiplex immunofluorescence will be prioritized over tumor for DNA extraction for T cell repertoire analysis.

7.2.3.2 Labeling of Specimens

All specimens will be labeled with the patient's unique study number and the time point of collection. Samples collected prior to initiating therapy with atezolizumab and nab-paclitaxel will be labeled "Pre", those obtained midway through treatment with atezolizumab and nab-paclitaxel will be labeled "Mid", and those obtained at the time of surgery will be labeled "Post". PBMC and serum samples obtained at the time of completion of atezolizumab treatment will be labeled "6 mo."

8.0 STUDY CALENDAR

The Study Calendar summarizes the study procedures to be performed at each visit. Due to scheduling, these visits can occur +/- 3 days from the required time point. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Pre-Surgery

Study Week (Pre-Surgery)		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Surgery**
Study Cycle		**1**			**2**			**3**			**4**			
Cycle Day	**-28 to 0**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Informed Consent	X													
Demographics	X													
Medical History	X													
General Physical	X	X[1]			X			X			X			
Vital signs[5], weight	X	X[1]			X			X			X			
Performance Status	X	X[1]			X			X			X			
Baseline Symptoms/Toxicity review	X	X[1]			X			X			X			
CBC	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	
aPTT and INR	X													
Chemistries/LFTs	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	
TSH, free T4, free T3	X	X[1]			X			X			X			
Pregnancy Test (serum or urine)	X[2]													
HBsAg, Anti HCV, EBNA IgG	X[8]													
Cardiac scan (MUGA or 2D ECHO)	X[3]													
Urinalysis	x													
Breast Ultrasound[6]	X							X						X
Core Biopsy	X[4]													X[7]
Surgical Specimen														X
Blood for PBMCs	X							X						X
Serum	X							X						X
Nab-paclitaxel		X	X	X	X	X	X	X	X	X	X	X	X	
Atezolizumab		X			X			X			X			

Post-Surgery

Study Week (Post-Surgery)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study Cycle	**5**			**6**			**7**			**8**			
Cycle Day	**1[9]**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
General Physical	X[1]			X			X			X			
Vital signs, weight	X[1]			X			X			X			X
Performance Status	X[1]			X			X			X			X
Baseline Symptoms/Toxicity review	X[1]			X			X			X			X
CBC	X[1]			X			X			X			X
Chemistries/LFTs	X[1]			X			X			X			X
TSH, free T4, free T3	X[1]			X			X			X			X
Blood for PBMCs													X
Serum													X
Atezolizumab	X			X			X			X			

1. If screening test was performed >10 days prior to the start of treatment, repeat test on Day 1
2. Serum or urine pregnancy test must be completes within 72 hours of starting the first dose of study medication
3. If ECHO or MUGA was performed >3 months prior to study, repeat test within the screening period
4. This biopsy is performed per the parent protocol 2014-0185. Up to 4 Core biopsies will be collected for this trial at the end of the anthracycline portion of the parent clinical trial
5. Please see section 6.1.1 for details
6. A window of +/- 7 days is given for ultrasounds as done per standard of care
7. An optional tumor biopsy will be obtained from patients who progressed while on atezolizumab+nab-paclitaxel prior to switching to the standard of care regimen of the physician's choice
8. As clinically indicated
9. Treatment with atezolizumab will resume within 4 weeks after surgery. The date of resumption will be the first day of the post-surgery (Day 1 of Cycle 5 post surgery).

The Principal Investigator or treating physician must review all lab results, determine clinical significance for abnormal labs, and sign and date the report.

Additional evaluations/testing may be deemed necessary by the Investigator and/or Genentech for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that

additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

If participating in the parent protocol, disease assessment will continue at least every 6 months for a total of 3 years. This assessment can be done by telephone as well by the research staff in Breast Medical Oncology if the patient is unavailable for local visits at The University of Texas MD Anderson Cancer Center and documented in the electronic medical record.

9.0 MEASUREMENT OF EFFECT

9.1 Response Criteria

For the purposes of imaging evaluation of tumor response for this study, the immune related response criteria (irRC) will be used as applicable:

irCR is complete disappearance of all lesions (whether measurable or not, and no new lesions).

irPR is a decrease in tumor burden > 50% relative to baseline

irSD is not meeting either of the above criteria and the absence of progression of disease

irPD is an increase in tumor burden, whereas Tumor Burden = the sum of perpendicular diameters (SPD) of the index lesion + SPD of any new measurable lesions, of > 25% relative to the minimum recorded tumor burden and confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

As this is a neoadjuvant study, the final assessment of response will be by pathological assessment and Residual Cancer Burden (RCB).

9.2 Disease-Free Survival

A secondary objective of this study is to estimate the PFS distribution. PFS is defined as the time from enrollment to progression of disease (> 20% increase in tumor size as defined in Section 10.1) or death whichever comes first.

9.3 Definition of Residual Cancer Burden

The RCB is a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. RCB can be divided into four classes (RCB-0 to RCB-III) and will be collected as part of the study.

RCB-0 (pCR), Minimal RCB (RCB-I), Moderate RCB (RCB-II), and Extensive RCB (RCB-III)

The following parameters are required from pathologic examination in order to calculate

Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")
    - If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative

sections from the largest cross- sectional area of primary tumor bed were submitted in cassettes A5 - A9")

3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

   0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

   - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
   - When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
   - Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.
   - e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

4. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:
   0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
5. The number of positive (metastatic) lymph nodes
6. The largest diameter (mm) of the largest nodal metastasis

The RBC can be accessed online: www.mdanderson.org/breastcancer_RBC.

10.0 ADVERSE EVENT REPORTING REQUIREMENTS

10.0 Assessment of Safety

Safety assessments will consist of monitoring and reporting AEs and SAEs per protocol. This includes all events of death, and any study-specific issue of concern.

10.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed in Study PCD4989g.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.[25] Recently, Hoffmann-La Roche (Genentech) has informed all study PIs of a newly identified risk, immune-related myocarditis. Myocarditis refers to a diverse group of heart-specific immune processes classified by a spectrum of clinical and histopathological manifestations. It may present as mild dyspnea or chest pain, or more severe cardiogenic shock or sudden death. In the absence of an infectious etiology, immune-related myocarditis is confirmed by histological evidence of inflammatory infiltrates within the myocardium, together with cardiac myocytes degeneration and necrosis of non-ischemic origin.

A more detailed safety profile of atezolizumab is provided in the atezolizumab Investigator's Brochure.

10.2 Safety Parameters and Definitions

10.2.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention

- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

10.2.2 Serious Adverse Events (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to atezolizumab.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- All adverse events will be recorded in the electronic medical record and scored with attributions. The PI or designee will be responsible for determined attributions. In addition to the medical record, all adverse events will be recorded in the REDCap database along with their determined attributions

Reporting to FDA:

• Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

10.3 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Boards (IRBs), and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

10.3.1 Adverse Event Reporting Period

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

After initiation of study drug all AEs and SAEs must be reported after informed consent is obtained and initiation of study treatment and until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

10.3.2 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its

duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab; and/or the AE abates or resolves upon discontinuation of atezolizumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than atezolizumab (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

10.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

10.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

10.4.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

10.4.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and

elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in REDCap.

10.4.2.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.4.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

10.4.2.5 Pregnancy

If a female subject becomes pregnant while receiving the study drugs or within 6 months after the last dose of study drug, a Pregnancy report CRF should be completed and expeditiously submitted (i.e., no more than 24 hours after learning of the pregnancy) to Genentech/Roche Drug Safety. Follow-up to obtain the course and outcome of the

pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drugs should be reported as an SAE. An investigator who is contacted by the patient may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

10.4.2.6 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after completing treatment with study drugs. Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy report CRF should be completed and expeditiously submitted to Genentech/Roche Drug Safety (i.e., no more than 24 hours after learning of the pregnancy).Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. Institutional procedures will be followed to possibly allow additional information on the course and outcome of the pregnancy to be collected. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

10.4.2.7 Abortions

Any abortion, whether accidental, therapeutic, or spontaneous, should be classified as an SAE (as the Investigator and Supporter consider abortions to be medically significant events), recorded in REDCap, and reported to Genentech/Roche Drug Safety expeditiously (i.e., no more than 24 hours after learning of the event).

10.4.2.8 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded in REDCap, and reported to Genentech/Roche Drug Safety expeditiously.

10.4.2.9 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior atezolizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

10.4.2.9a Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x ULN) in combination with either an elevated total bilirubin (> 2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN

Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event CRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest.

10.4.2.10 Safety Reconciliation

The Sponsor-investigator agrees to conduct case transmission verification reconciliation for the product ensure that all single case reports have been adequately received by Genentech/Roche, via the exchange of a periodic line-listing documenting single case reports sent by the sponsor in the preceding month. Following reconciliation, single case reports which have not been received by Genentech/Roche shall be forwarded by the sponsor-investigator to Genentech/Roche within FIVE (5) CALENDAR DAYS from request by Genentech/Roche

10.4.2.11 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP.

The following AEs are considered of special interest and must be reported to the Genentech/Roche Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency or hyperthyroidism
- Hepatitis
- Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) or AST/ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Myasthenia gravis

- Meningoencephalitis
- Nephritis

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic inflammatory activation or infusion-reaction syndromes
- Suspected Transmission of Infectious Agent via Medicinal Product (STIAMP)

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

  Adverse Events of special interest will be reported to the IND office via eSAE application. The form completed for IND reporting will be forwarded to Genentech for reporting purposes.

Communications between the Investigator and Supporting Company

Investigators must report all SAEs to Genentech/Roche within the timelines described below. The completed MDA SAE should be faxed immediately upon completion to Genentech/Roche Drug Safety at:

E-mail: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

SAE reports and AESIs, whether related or unrelated to atezolizumab, will be transmitted to Genentech/Roche within 24 hours of the Awareness Date.

- Non-serious AEs

The investigator will forward a copy of the Final Study Report to Roche upon completion of the Study. In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Roche even in the absence of an Adverse Event within 1 business day of awareness date:

- Data related to product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy

Note: Investigators should also report events to their IRB as required.

10.4.3 Additional Reporting Requirements for IND

For investigator-initiated IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report

The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of atezolizumab. An unexpected AE is one that is not already described in the atezolizumab Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab. An unexpected AE is one that is not already described in the atezolizumab Investigator's Brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Contact Information for IND Safety Reports

FDA fax number for IND safety reports:

Fax: (800) FDA-0178

All written IND safety reports submitted to the FDA by the investigator must also be faxed to the following:

Roche Drug Safety

E-mail: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

The University of Texas MD Anderson Cancer Center IRB

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

Reporting to the FDA is done through the institutional IND office, as detailed in section 10.2.2

10.4.4 IND Annual Reports

Copies of all IND annual reports submitted to the FDA should be sent by the Investigator to Genentech/Roche Drug Safety via e-mail:
Email: anti-pdl-1-mpd3280a-gsur@gene.com

10.5 Study Close-Out

Any study report submitted to the FDA should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab Protocols
Email: anti-pdl-1-mpd3280a-gsur@gene.com

10.6 Study Medication Accountability

The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

10.7 Product Complaint

Product complaint information provided orally or in writing from a complaint that alleges deficiencies related to identity, quality safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial will be reported as follows;

Product complaint **with AE (adverse event)** should be reported via email/fax to usds_aereporting-d@gene.com or 650-238-6067

Product complaint **without an AE** should be reported to kaiseraugst.global_impcomplaint_managment@roche.com

All complaint must be filed within 1 business day for pre-approved products and 15 calendar days for approved products.

Complaints can be reported using Med Watch, CIOMS or any Genentech approved reporting form (same as SAEs, AESI, etc.).

11.0STATISTICAL ANALYSIS PLAN

11.1 Statistical Analysis Plan Summary

Counting pCR (RCB-0) or RCB-I as response, we will employ a two-stage Gehan-type design with 19 patients in the first stage. If at least one patient responds, we will add 18 more patients for a total of 37 patients. This design has a 38% chance of terminating after the first stage if the true response rate is 0.05, 14% chance if the true rate is 0.10, 5% if the true rate is 0.15 and 1% if the true rate is 0.20. If we continue to the second stage and enroll a total of 37 patients, the exact 95% confidence interval for a 0.15 response rate will extend from 0.05 to 0.31.

We will estimate the proportion of patients with pCR (RCB-0) or RCB-I as the response rate along with an appropriate 95% confidence interval. We will estimate the proportion of patients in the remaining RCB categories with confidence intervals as well. We will estimate the PFS distribution using the Kaplan-Meier method from the date of enrollment onto this study until the date of progression or death without evidence of progression. Patients alive and disease-free at the latest clinical evaluation will be censored at the date of that evaluation. We will also estimate the OS distribution in a similar fashion.

Early drop outs (i.e., patients not getting to surgery) should be counted as treatment failures (i.e., non-responders with RCB > 1).

A response summary will be submitted to the IND Medical Monitor after treatment of the 19th patient has completed.

If no RCB-0 or -1 response has been observed prior to enrolling the 20th patient, enrollment will stop until all of the 19 patients in the first stage are evaluable and resume only if a response has been documented.

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