CUMC IRB#:	AAAQ3153
Celgene Protocol Identifier	AX-CL-NSCLC-PI-005652
Genentech Protocol Identifier	ML29820
Version Date:	05-SEP-2018
TITLE:	A single-arm, phase II study of neoadjuvant MPDL3280A, *nab*-paclitaxel and carboplatin (MAC) in resectable non-small cell lung cancer
Coordinating Center:	Columbia University Medical Center

Principal Investigator:
Catherine Shu
161 Fort Washington Avenue
New York, NY 10032
Telephone: 212-305-3997
Fax: 212-305-3035
cas2145@cumc.columbia.edu

Statistician:
Codruta Chiuzan, PhD
722 W 168th St., 6th Floor
New York NY 10032
Telephone: 212-305-9701
Fax: 212-305-9408
cc3780@cumc.columbia.edu

Regulatory Sponsor:	Columbia University Medical Center 161 Fort Washington Avenue 212-305-3997 New York, NY 10032
Funding Source:	Genentech-BioOncology 1 DNA Way Mailstop 258A South San Francisco, CA 94080 (888) 662-6728 Celgene Corporation Attn: Medical Affairs Operations Connell Corporate Park 400 Connell Drive Suite 700 Berkeley Heights, NJ 07922 (908) 673-9000

Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (Print)

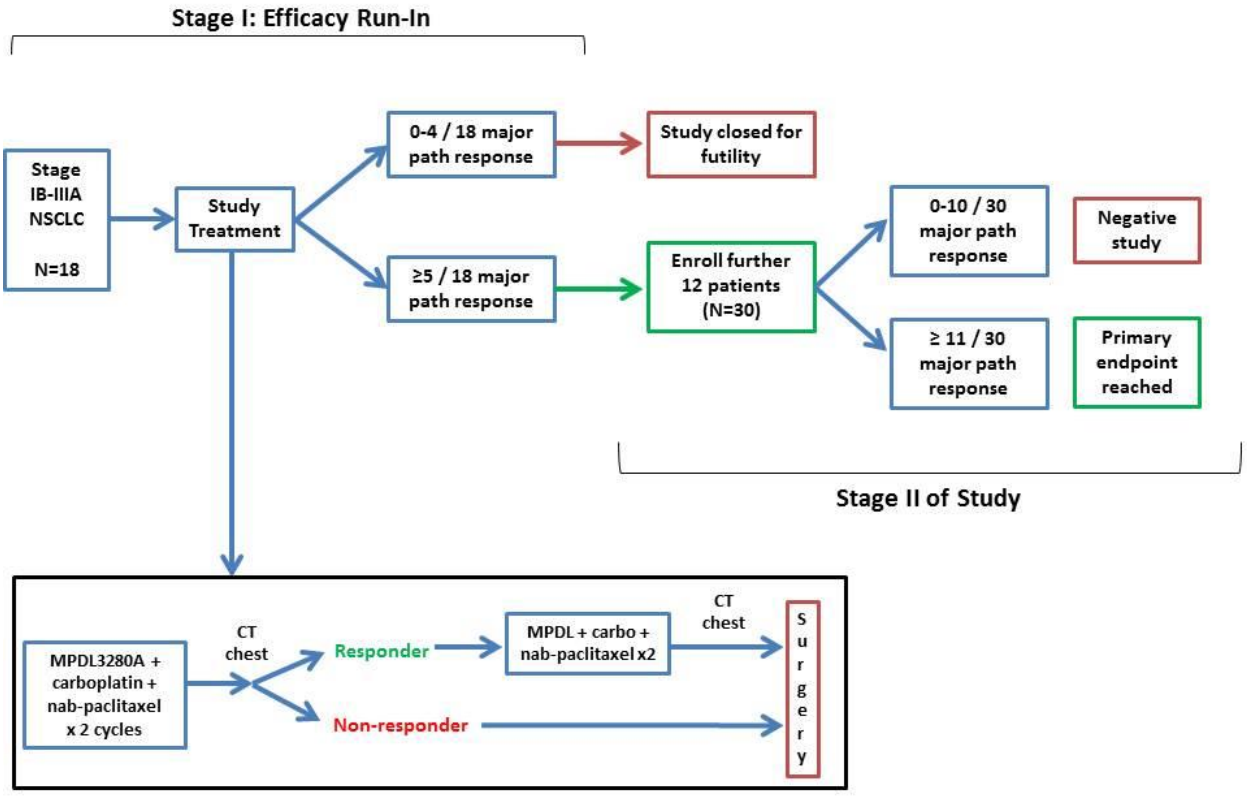
_____

Name of Institution

Protocol Synopsis

Title	A single-arm, phase II study of neoadjuvant MPDL3280A, *nab*-paclitaxel and carboplatin (MAC) in resectable non-small cell lung cancer (NSCLC)
Short Title	Neoadjuvant MPDL3280A, nab-paclitaxel and carboplatin in NSCLC
Protocol Number	AAAQ3153
Celgene Protocol Identifier	AX-CL-NSCLC-PI-005652
Genentech Protocol Identifier	ML29820
Phase	Phase II
Methodology	Two-stage trial design with a target accrual of 33 patients, with a goal of 30 evaluable patients: Stage 1: 18 evaluable patients accrued with pre-defined efficacy and safety stoppage criteria Stage 2: Additional 12 evaluable patients accrued
Study Duration	36-48 months
Study Center(s)	Multi-center, anticipating enrollment at Columbia University Medical Center, and Dana Farber-Harvard Cancer Center (Massachusetts General Hospital & Dana Farber Cancer Institute).
Objectives	1. To determine the activity of neoadjuvant MAC, as determined by major pathologic response rate (MPR), in comparison with an historical control rate. 2. To measure the activity of neoadjuvant MAC by objective response, disease free survival, and overall survival 3. To determine the safety and feasibility of MAC in the neoadjuvant setting for stage IB, II, and IIIA NSCLC 4. To explore the immune effects of MAC as determined by IHC analysis of immune and T cell subsets.
Number of Subjects	Stage 1: 18 patients Total at study closure: 30 evaluable patients
Diagnosis and Main Inclusion Criteria	Resectable stage IB-IIIA NSCLC Smoking history
Study Product, Dose, Route, Regimen	MPDL3280A, 1200 mg IV Day 1 every 21 days Carboplatin, IV, AUC=5 Day 1 every 21 days nab-paclitaxel, IV, 100 mg/m2 Day 1, 8 and 15 every 21 days
Duration of administration	Four 21 day cycles prior to surgery
Reference therapy	Historical, this is a single arm study

Statistical Methodology	α=0.05, power=0.83 to detect an increase in MPR from 22% (historical control) to 44%. The remainder of the analysis is exploratory.



- Responder refers to a patient with disease control (defined as CR, PR, or SD)
- Non-responders have PD as their best response

Contents

INTRODUCTION

Lung cancer is the most common cancer in both men and women worldwide, accounting for 13% of incident cancers.[1] In 2015, it was estimated there would be 221,200 new lung cancers diagnosed in the United States, with 158,040 lung cancer deaths.[2] Approximately 85% of all lung cancers are characterized as non-small cell lung cancer (NSCLC).[3] Adenocarcinoma histology accounts for the majority of NSCLC, while squamous histology comprises a further 25%.[4] Other histologies, including large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated tumors collectively comprise only 15% of NSCLC.

The 5 year survival of stage IB-IIIA NSCLC is only 19-43% and systemic recurrence occurs in the majority of patients.[5] Randomized multi-modality trials have demonstrated a 10-30% survival advantage with the use of adjuvant or neoadjuvant chemotherapy over surgery alone. The benefits of platinum-based adjuvant chemotherapy were conclusively demonstrated in the Lung Adjuvant Cisplatin Evaluation meta-analysis, which incorporated five large clinical trials using a variety of treatment regimen.[6] In the pooled analysis of 4584 patients with stage I-III NSCLC, followed for a median of 5.2 years, adjuvant cisplatin-based chemotherapy improved overall survival with a hazard ratio (HR) of 0.89 (95% CI 0.82-0.96). The effect was most pronounced for stage II (HR 0.83, 95% CI 0.73-0.95 and III disease (HR 0.83; 95% CI 0.72-0.94), with a trend toward effect for stage IB and no effect seen for stage IA. These findings were confirmed in another meta-analysis of 2660 patients undergoing NSCLC resection alone, although these findings translated to just a 4% improvement in 5-year survival to 33% overall.[7]

Similar to adjuvant chemotherapy, the survival benefits of neoadjuvant platinum-based chemotherapy (NCT) (death HR 0.87, 95% CI 0.78-0.96; 5% improvement in 5-year survival) were published in a meta-analysis of 15 randomized controlled trials evaluating patients with predominantly stage IB-IIIA NSCLC.[8] Of note, several of the trials in that analysis were closed early once the outcomes of adjuvant therapy trials were published. As a result of this study, neoadjuvant platinum-based chemotherapy for surgically resectable NSCLC is a widely accepted alternative to adjuvant chemotherapy.

1. STUDY OBJECTIVES

This is an open-label, multi-center, single-arm, phase II study of neoadjuvant MPDL3280A. nab-paclitaxel and carboplatin administered for 4 cycles. The target population includes patients with pathologically confirmed stage IB-IIIA NSCLC. This study aims to determine if chemotherapy + anti-PD-L1 antibody therapy is safe and feasible in the preoperative setting. We will also explore the efficacy of the combination in the preoperative setting. Eligible patients must have surgically resectable tumors. Excluded patients include those who have previously been treated with T-cell checkpoint inhibitors, those with auto-immune disease, concurrent treatment with alternative anti-cancer therapy or systemic immunosuppressants. Adjuvant treatment with chemotherapy and radiation therapy will be determined based on the results of surgery and as determined by the treating investigator.

Patients must be determined to have surgically resectable disease. Excluded patients include never-smokers, those who have previously been treated with T-cell checkpoint inhibitors, those with auto-immune disease, concurrent treatment with alternative anti-cancer therapy or systemic immunosuppressants.

Patients will receive 2 cycles of MPDL3280A and carboplatin on D1 and nab-paclitaxel D1, D8, and D15 both every 21 days followed by a re-imaging CT scan to assess response. Patients with an objective response or stable disease by RECIST v1.1 and acceptable toxicity will receive an additional 2 cycles followed by standard restaging scans and then surgery. Patients with progressive disease by RECIST v1.1 after the first 2 cycles of treatment will proceed directly to surgery.

The study will accrue a maximum of 30 evaluable patients with early stopping rules for treatment related toxicities. An interim evaluation after enrollment of 18 patient will be performed with pre-defined stoppage criteria for lack of efficacy (MPR in 4 or fewer patients). If at any time more than 2 patients experience severe drug-related toxicity (not progression) that prohibits or significantly delays planned surgery, the study will be closed. Patients will receive standard postoperative therapy as determined by the treating physician, but not as part of this study. Following surgery, patients will be followed with standard CT scans of the chest with contrast, as well as routine and exploratory blood tests every 3 months, until 6 months after surgery or until resolution of all treatment related toxicities to grade ≤1.

Efficacy endpoints that will be assessed include radiologic response by RECIST v1.1, pathologic response, nodal downstaging, DFS and OS. Exploratory endpoints will be measured in pre and post-therapy blood and surgical specimens, including: immune ligand expression, T-cell phenotype in tumor and tumor-infiltrating lymphocytes (TILs). Safety endpoints will also be continuously assessed.

1.1 Primary Objectives

- To evaluate the activity of neoadjuvant MAC in patients with NSCLC as measured by major pathologic response rate (MPR) defined below as > 90% decrease in viable tumor)

1.2 Secondary Objectives

- To determine the objective response rate, disease free survival, and overall survival of subjects with stage IB-IIIA NSCLC treated with neoadjuvant MAC.
- To evaluate the safety and feasibility of neoadjuvant MAC in subjects with resectable stage IB-IIIA NSCLC
- To detect alterations of tumor immune microenvironment pre-and post-treatment (PD-L1, PD-L2, TIM3, LAG3 and T cell subsets (CD3, CD8, Tregs).

2. BACKGROUND

2.1 Rationale for neoadjuvant therapy in resectable NSCLC

Repeated studies have shown neoadjuvant cytotoxic chemotherapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality.[9-12] Objective response rates to neoadjuvant chemotherapy range from 40-70%, with rates of pathologic complete response of 6-12% with standard chemotherapy regimens used in NSCLC.[10,13-17]

In 2009 Lim *et al*.[18] published an indirect comparison meta-analysis to obtain the relative hazards of post-operative to pre-operative administration of chemotherapy on survival. Data from 32 randomized trials involving 10,000 participants were included. There were more trials in the postoperative group (n=22) compared to the preoperative group (n=10) demonstrating the weight of evidence in existence for postoperative chemotherapy. For overall survival, the relative hazard ratio of postoperative compared to preoperative chemotherapy was 0.99 (95% CI: 0.81-1.21, P=0.91). For disease free survival the findings were similar with a relative hazard ratio of 0.96 (95% CI: 0.77-1.20, P=0.70).

The debate remains as to whether neoadjuvant or adjuvant chemotherapy is the best approach, with advantages and disadvantages to each. Adjuvant treatment has the advantage of providing clinicians with a pathologic stage to guide postoperative therapy recommendations. While upfront surgery guarantees adequate tissue for molecular studies, current targeted therapies (such as erlotinib in EGFR-mutant NSCLC) remain investigational in the adjuvant setting and are being studied only after completion of standard therapies. The main disadvantage of adjuvant chemotherapy is the difficulty of drug delivery postoperatively. For clinical investigation, administration of neoadjuvant chemotherapy allows for an in vivo assessment of treatment response radiologically and pathologically, and the use of surrogate endpoints such as downstaging and pathologic response. The use of neoadjuvant therapy followed by surgery has the advantage of allowing administration of 90% of planned cisplatin-based chemotherapy compared with 50% of planned treatment in the post-operative setting without any increase in surgical risk. This approach provides earlier systemic therapy for the treatment of micrometastatic disease and allows for an assessment of treatment efficacy in each individual patient. In addition, sterilization of N2 disease with neoadjuvant chemotherapy can obviate the need for adjuvant radiation therapy. Neoadjuvant therapy also allows for an in vivo evaluation of new therapeutic approaches, providing critical information for drug development as response to therapy can be assessed both radiographically and correlatively in post-treatment pathologic specimens.

Clinical trials in resectable lung cancer have traditionally attempted to institute new agents in the adjuvant setting. However, significant co-morbidities and incomplete recovery from surgery contribute to a high proportion of patients who are unable to tolerate adjuvant therapy. Additionally, clinical endpoints take years of follow-up to ascertain. The BLOT (Bimodality Lung Oncology Team) study was a large phase II study that compared neoadjuvant to adjuvant carboplatin and paclitaxel in 134 patients with stage IB-IIIA disease. In this study, 51% of

patients who received neoadjuvant chemotherapy had an objective response, and 7% had a pathologic complete response. In this study, 97% of patients in the neoadjuvant group completed chemotherapy versus 31% of patients in the adjuvant group.[19] Following this, the phase III NATCH trial compared surgery alone versus surgery + preoperative, versus surgery + postoperative therapy, with carboplatin and paclitaxel. In this study, 90% of the preoperative cohort completed therapy versus 66% of the post chemotherapy group[12].

Taken together, these trial results demonstrate that it is easier to deliver therapy in the neoadjuvant setting, with a higher proportion of patients completing neoadjuvant compared to adjuvant therapy. In addition, such an approach is an *in vivo* test of sensitivity to therapy that is positively associated with improved outcomes, and has the potential to eradicate micrometastatic disease prior to surgery.

In addition to these benefits, a neoadjuvant approach has practical benefits of yielding results over a shorter time period compared to trials carried out in the adjuvant setting. Two reasons for the slow progress of adjuvant studies in resectable NSCLC are the technicalities of using multimodality therapy in this setting, and the long wait for results with survival endpoints. The ANITA study was a phase III study of adjuvant chemotherapy in NSCLCs.[20] In this study, results were published 12 years after study initiation. Thus, while OS remains the gold standard for assessment of benefit of adjuvant therapy, studies that are 12 years long are slow, expensive, and may yield results that are out of date by the time they are published. The use of a valid surrogate endpoint for OS is thus a high priority in NSCLC. An example of such an endpoint includes 3-year disease-free survival (DFS), which correlates with 5-year OS. However, in the context of the ANITA study, a 3-year DFS endpoint would have taken 9 years to be reached. This issue is borne out in other solid tumors as well, with the reporting of 3-year DFS in adjuvant colon cancer taking 8 years to mature.[21-23] Thus a surrogate endpoint which can be achieved in a shorter timeframe is needed in NSCLC.

In resectable breast cancer, the use of neoadjuvant chemotherapy creates an efficient and effective surrogate endpoint of pathologic complete response (pCR), that correlates with both DFS and OS across multiple randomized studies, and is thus used as a surrogate endpoint for survival in this disease.[24-30]

The degree of pathologic response seen in lung cancer following neoadjuvant chemotherapy, is termed a major pathologic response (MPR, ≤10% residual viable tumor cells).[31] MPR has been found to directly reflect the impact of NCT in NSCLC, with the magnitude of MPR reflecting magnitude of improvement in overall survival.[32] MPR also associates with disease-free survival. Results from prospective studies by Betticher[33] and Chaft[34] both report that 22% of patients with stage I-IIIA NSCLCs treated with NCT achieved a MPR. Historical reports of cisplatin-based NCT estimates major pathologic response rates of 10-15%.[35] We propose “major pathologic response” (MPR), defined as ≤10% residual, viable tumor in the resected tissue sample at the time of surgery, as an assessable and reliable surrogate measurement of survival[36]. As has been demonstrated in breast cancer, a broad acceptance of such as surrogate has the potential to substantially expedite conclusions from clinical trials and improvements in clinical practice for patients..

With the above data in mind, we propose that new therapies such as immune checkpoint inhibitors that demonstrate promising clinical activity in the advanced disease setting must be incorporated into the neoadjuvant setting, in order to maximize benefit early in a patient's treatment course, and with a suitable surrogate endpoint that can be used to establish a preliminary efficacy signal, prior to initiation of a large confirmatory study.

2.2 Rationale for surrogate biomarkers of benefit

While disease free and overall survivals remain the gold-standard for evaluation of perioperative interventions, surrogate endpoints can provide an earlier estimation of the effectiveness of new therapies. Hellmann and colleagues (2014) proposed that pathological response after treatment for resectable NSCLCs can serve as a surrogate for OS. This proposal was based on the US Food and Drug Administration's (FDA) definition of a surrogate endpoint in the accelerated drug approval process, where such an endpoint is defined as one that is 'reasonably likely to predict clinical benefit.' Neoadjuvant chemotherapy in lung cancer demonstrates that: (a) the extent of pathological response strongly correlates with improved overall survival; (b) the pathological response is reflective of the effect of neoadjuvant therapy; and (c) the degree of pathological response associates with the degree of benefit in overall survival.[32]

Major pathologic response is defined as treatment effect of more than 90% (MPR, ≤10% residual viable tumor cells). Junker, et al.[37] described pathological response as predictive of outcomes after multimodality therapy, with patients with <10% viable tumor cells remaining experiencing the best outcomes. In a more recent publication of 192 patients with NSCLC who received neoadjuvant chemotherapy, the long term OS and RFS of the 19% of patients with tumors demonstrating ≥90% pathological response were significantly different than those with <90% response.

MPR directly reflects the impact of chemotherapy and the magnitude of MPR reflects the magnitude of improvement in overall survival. MPR also associates with disease-free survival. Results from prospective studies by Betticher[33] and Chaft[34] both report that 22% of patients with stage I-IIIA NSCLCs treated with neoadjuvant chemotherapy achieved a MPR. We propose "major pathologic response" (MPR), defined as ≤10% residual, viable tumor in the resected tissue sample at the time of surgery, as an assessable and reliable surrogate measurement of survival. As had been demonstrated in breast cancer, a broad acceptance of such as surrogate has the potential to substantially expedite conclusions from clinical trials and improvements in clinical practice for patients. A standardized approach to assessment of percentage of viable residual disease after neoadjuvant chemotherapy is as described by Pataer and colleagues[31] (see Section 12.1).

Complete pathologic response (CPR) refers to the eradication of any detectable cancer within the surgically resected lung specimen and lymph nodes. Of 15 trials which reported CPR, the median rate is just 4% (range 0-16%) (Hellmann 2014). Few trials have reported corollary survival data for NSCLC due to the low frequency of CPR. One retrospective review of 9 patients with CPR observed a remarkable 54% overall survival.[10] Combined data from 2 phase III trials in Stage Ib-

II NSCLC revealed 41 patients (8.3% of total) with CPR had a 5-year DFS 80.1% vs 44.8% for the non-CPR group ($p<0.0001$) and 5-year overall survival 80% vs 56% ($p<0.01$).[38] Given the low frequency of CPR, it is not likely to be a feasible endpoint for neoadjuvant clinical trials in NSCLC.

2.3 Rationale for neoadjuvant immune checkpoint blockade

Immune based therapies which enhance the host anti-tumor immune response are a promising therapeutic strategy in NSCLC. Programmed death-1 (PD-1 or CD279), is a transmembrane receptor protein that functions as a CD28 co-stimulatory molecule on the surface of T cells.[39] Upon binding to ligands PD-L1 and PD-L2, T-cell activation is inhibited by suppressing CD28 mediated increases in IL-2, IL-10, IL-13, IFN-gamma, and Bcl-xL.[39-43] In human cells, constitutive PD-L1 expression is normally limited to macrophages, while it remains inducible in other cells. Aberrant expression of PD-L1 by tumor cells enhances apoptosis of nearby activated tumor-specific T cells and simultaneously prevents T cells from inducing apoptosis of malignant cells *in vitro*.[43,44]

In clinical studies, immune checkpoint inhibitors, including those which target CTLA-4, PD-1, and PD-L1, can reverse immune tolerance to cancer specific antigens.[45,46] Agents targeting the PD-1/PD-L1 interaction enhance the host anti-tumor T-cell response. Many of these agents are active against NSCLC in the metastatic setting.[47-50] In a phase II single-arm, single agent trial of nivolumab in 117 patients with advanced squamous NSCLC, the OR was 14.5% by RECIST v1.1, and an additional 26% of patients had stable disease.[51] In a separate study of 129 patients with heavily pre-treated, advanced NSCLC, the response rate was 22% (17% by RECIST v1.0, 5% with delayed immune-pattern response) and treatment was generally well tolerated.[47]

Ipilimumab, an anti-CTLA-4 antibody, is the first checkpoint inhibitor to demonstrate a clinical benefit in a phase III trial when administered in the perioperative period for any cancer, in this case given adjuvant for melanoma.[52] Patients with early stage bladder cancer have been treated with neoadjuvant ipilimumab in a phase I study.[35] Neoadjuvant ipilimumab was found to have a tolerable safety profile without an increase in perioperative complications after 1 or 2 doses of neoadjuvant therapy. Valuable information on the immunological effects of ipilimumab was gleaned from studying the resected bladder tumors in these patients. A recent publication with neoadjuvant ipilimumab in patients with surgically operable regionally advanced melanoma demonstrated pathologic response in a subset of melanoma patients.[53] Patients were treated with ipilimumab (10 mg/kg intravenously every 3 weeks ×2 doses) before surgery. Twenty-one patients (64%) had stable disease and eight patients (24%) had disease progression. All patients had histologically documented residual melanoma at definitive surgery following 2 doses of ipilimumab, although 5 patients had only microscopic disease detected. Additionally in advanced melanoma treated with combination CTLA-4/PD-1 blockade major responses (80% tumor reduction) and complete responses were observed in 30 and 10% of patients.[54]

Unpublished data from WCLC 2013 (Gettinger et al) has also shown case reports of resection samples of residual disease after a PD-L1 antibody (MPDL3280A) with only minimal residual disease.

All of the above point to the potential for inducing pathologic response with immune checkpoint blockade.

2.4 Rationale for neoadjuvant nab-paclitaxel and carboplatin

nab-paclitaxel + carboplatin is an FDA approved chemotherapy doublet used in the first-line treatment of advanced NSCLC. In the advanced setting, the combination of carboplatin, administered at an AUC 6 every 3 weeks of a 21 day cycle, combined with nab-paclitaxel 100mg/m2 weekly vs. standard carboplatin plus solvent based paclitaxel administered every 21 days has been studied . Administration of *nab*-PC as a first-line therapy resulted in a significantly improved ORR versus sb-PC (33% *v* 25%; *P* = .005) thereby achieving the primary end point. Nonsignificant improvement was observed in favor of the *nab*-PC arm for PFS or OS, meeting noninferiority criteria. The *nab*-PC regimen produced less severe neuropathy, neutropenia, myalgia, and arthralgia compared with sb-PC.[55]

The NATCH trial[12] evaluated carboplatin + paclitaxel as either adjuvant or neoadjuvant therapy for resectable, stage IA-IIIA NSCLC. Three year PFS was higher in the neoadjuvant group (48.4%) than either the adjuvant group (44.9%) or the surgery alone group (41.9%) although these results were not statistically significant. Treatment was generally well tolerated, with similar surgical mortality (5-7%) between groups. In the neoadjuvant arm, the pCR rate was 10.5%, and the ORR by RECIST was 53.3% including 9% CR.

A neoadjuvant trial for stage IB to IIIA NSCLC evaluated carboplatin, AUC6, every 21 days and paclitaxel 80 mg/m weekly and in 20 patients demonstrated a complete pathologic response rate of 17%.[56]

2.5 Rationale for neoadjuvant MPDL3280A and nab-paclitaxel + carboplatin

MPDL3280A targets PD-L1 with good single agent activity against NSCLC in the advanced setting . Tumor cell killing by cytotoxic chemotherapy can reasonably 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 with standard chemotherapy alone.[57,58] In preclinical experiments, traditional chemotherapies have been shown to augment the host anti-cancer immune response as well as disrupt immune evasion by cancer cells.[59] Evaluating the safety and efficacy of these treatment combinations in NSCLC patients will enable future tests of this hypothesis.

Nivolumab, a fully human IgG4 PD-1 antibody, was evaluated in combination with platinum-based doublet therapy in PD-1−unselected, chemotherapy-naïve NSCLC patients, and interim results were presented at ASCO 2014.[60] The ORR for patients treated with gemcitabine+

cisplatin, pemetrexed+ cisplatin, and paclitaxel + carboplatin, in addition to 10 mg nivolumab, was 33% (n= 12), 47% (n = 15), and 47% (n= 15), respectively. The median duration of response ranged from 24 weeks with nivolumab in combination with paclitaxel + carboplatin to 45 weeks with nivolumab in combination with gemcitabine + cisplatin. The 1-year OS for patients treated with gemcitabine+ cisplatin, pemetrexed + cisplatin, and paclitaxel + carboplatin in addition to 10 mg nivolumab was 50%, 87%, and 60%, respectively. Grade 3/4 treatment-related adverse events were reported in 45% of patients across all treatment arms with the most common treatment-related Grade 3/4 adverse events being pneumonitis (7%), fatigue (5%), and acute renal failure (5%).[60]

The combination of MPDL3280A with carboplatin based chemotherapy was specifically evaluated in 37 patients with advanced NSCLC in the phase Ib GP28328.[61] MPDL3280A was added to carboplatin with either paclitaxel, nab-paclitaxel, or pemetrexed. In the nab-paclitaxel arm (n=15), the regimen was well-tolerated with the most common AEs attributed to the cytotoxic agents being nausea (73%), fatigue (73%), and constipation (27%). Severe toxicity was uncommon: grade 3-4 anemia (7%), thrombocytopenia (7%), and no neutropenia nor pneumonitis. The ORR was 62% (33-83%) with 6 PRs and 2 CRs. Safety and efficacy were comparable across all study arms, and no patient required steroid treatment. Responses were seen independent of PD-L1 expression.

2.6 Rationale for exclusion of never-smokers

The rationale to exclude never-smokers is two-fold. The first reason is to exclude those who are most likely to have an actionable oncogene driver mutation identified in their tumor, such as *EGFR* or *ALK*. Due to small diagnostic samples and timeline of neoadjuvant therapies, molecular results are often not available when neoadjuvant treatment begins. Excluding never-smokers will exclude the majority of those who have an *EGFR* or *ALK* mutation and may be eligible to receive an adjuvant targeted therapy as part of the upcoming cooperative group trials. Secondly, preliminary experience in the assessment of benefit from T-cell checkpoint blockade in patients with advance disease suggests a better benefit is obtained in smokers. In analysis of data from treatment with nivolumab (anti-PD-1 mAb), the response rate and progression-free survival in current or former smokers was significantly greater than never or minimal smokers (≤5 pack-years) (response rate 30% vs 0%, p=0.02; HR for PFS 0.41, p=0.003).[51] Similar findings were observed with pembrolizumab in the large phase I study KEYNOTE-001.[62] Among 495 patients who received treatment, the response rate in smokers was 22.5% as compared with 10.3% in never smokers. We therefore have opted to exclude never-smokers from this trial.

3. INVESTIGATIONAL AGENT

MPDL3280A 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. MPDL3280A 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. MPDL3280A targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). MPDL3280A also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

3.1 Preclinical Data

Comprehensive pharmacology, PK, and toxicology evaluations have been undertaken with MPDL3280A.

The safety, pharmacokinetics, and toxicokinetics of MPDL3280A 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 MPDL3280A 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 MPDL3280A.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for MPDL3280A 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.

For further details please refer to the investigator brochure for MPDL3280A.

3.2 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03−20 mg/kg), MPDL3280A 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 (CL) 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 the detection of ATAs and adverse events or infusion reactions has been observed.

3.3 MPDL3280A Dosage

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

The target exposure for MPDL3280A was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed MPDL3280A interim pharmacokinetics in humans, and other factors. The target trough concentration (Ctrough) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The MPDL3280A dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of MPDL3280A was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg MPDL3280A q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain Ctrough ≥6 μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of MPDL3280A relative to the 10-mg/kg MPDL3280A q3w regimen (or fixed-dose equivalent). From inspection of available observed Ctrough data, moving further to the 20-mg/kg MPDL3280A q3w regimen does not appear to be warranted to maintain targeted Ctroughlevels relative to the proposed 15-mg/kg MPDL3280A q3w level.

Simulations (Bai 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. Therefore, a fixed dose of 1200 mg has been selected (equivalent to an average body weight−based dose of 15 mg/kg). Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation. Refer to the MPDL3280A Investigator's Brochure for details regarding nonclinical and clinical pharmacology of MPDL3280A.

3.4 Clinical Data to Date

Efficacy analyses are currently available for 386 patients with measurable disease at baseline and at least 6 months of follow-up in the phase Ib study PCD4989g (unpublished data). Patients with multiple tumor types were included in the study, with the largest cohorts consisting of patients with NSCLC, RCC, and bladder cancer. Objective responses with MPDL3280A monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer and sarcoma. Altogether, 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. Herbst et al.[49] reported that 11/53 (21%) patients with advanced NSCLC experienced at least a partial response with single agent therapy at a variety of doses. The percentage of patients with no disease progression at 24 weeks was 45%.

Analyses of tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g, in which MPDL3280A is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to MPDL3280A.

3.5 Safety Data to Date

Interim safety data for single agent MPDL3280A are available from PCD4989g. In 412 treated patients, 97.1% reported an AE while on study. Of these AEs, 48.8% were Grade 1 or 2 in maximum severity on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed AEs (occurring in ≥ 10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, and upper respiratory tract infection. Grade ≥ 3 AEs were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade ≥ 3 AEs that were assessed as related to study drug by the investigators. The most frequently reported related Grade ≥ 3 AEs included fatigue (5 patients [1.2%]), increased ALT and increased AST (each reported in 4 patients [1.0%]); and asthenia, autoimmune hepatitis, and hypoxia (each reported in 3 patients [0.7%]).

Herbst et al.[49] reported on 277 patients with incurable cancers who received MPDL3280A alone every 3 weeks. Treatment was well tolerated at doses up to 20mg/kg. Systemic inflammatory markers IFN-gamma and CD8+/HLA-DR+/Ki-67+ were elevated approximately 2-fold with treatment. Fatigue (67%) was the most common adverse event and typically co-occurred with pyrexia (~21%) only during the first cycle. Treatment-related grade 3-4 adverse events (AEs) were observed in 13% of patients, and just 3 patients (1%) experienced grade 3-4 immune related AEs (irAEs). The majority of grade 3+ AEs involved lab abnormalities of uncertain significance: AST/ALT elevation (6 events), hyperglycemia (2), hyponatremia (2), hypophosphatemia (2), and tumor lysis syndrome (2). There were two cases of cardiac tamponade and no cases of grade 3-5 pneumonitis.

3.6 Other Agent(s)

Nab-paclitaxel + carboplatin is an FDA approved chemotherapy doublet used in the first-line treatment of advanced NSCLC. In the advanced setting, the combination of carboplatin, administered at an AUC 6 every 3 weeks of a 21 day cycle, combined with nab-paclitaxel 100mg/m2 weekly vs. standard carboplatin plus solvent based paclitaxel administered every 21 days has been studied. Administration of *nab*-PC as a first-line therapy resulted in a significantly improved ORR versus sb-PC (33% *v* 25%; *P* = .005) thereby achieving the primary end point.

Nonsignificant improvement was observed in favor of the *nab*-PC arm for PFS or OS, meeting noninferiority criteria. The *nab*-PC regimen produced less severe neuropathy, neutropenia, myalgia, and arthralgia compared with sb-PC.[55]

4. STUDY DESIGN

4.1 Study Design

This is an open-label multi-center, single-arm, phase II study of neoadjuvant nab-paclitaxel + carboplatin + MPDL3280A administered for 4 cycles. The target population includes patients with a smoking history and pathologically confirmed clinical stage IB-IIIA NSCLC. The study aims to determine if chemotherapy combined with immune checkpoint blockade can lead to improvement in major pathologic response rates over historic controls with platinum doublet based chemotherapy alone. Such historical rates approach 22%, as recently reviewed by Pataer, et al.[31] The study will accrue 30 evaluable patients, and will be performed in a two-stage design, with an interim assessment for efficacy after 18 patients, and early stopping rules for pre-defined toxicities (see Section 12.9). Adjuvant treatment with chemotherapy and radiation therapy will be determined based on the results of surgery and at the discretion of the treating investigator.

4.2 Primary Endpoints

The primary outcome measure is major pathologic response (MPR) in NSCLC samples at the time of surgery.

4.3 Secondary Endpoints

Secondary efficacy endpoints include overall response rate (ORR) per RECIST v1.1, disease free survival (DFS) and overall survival (OS). Secondary exploratory goals will include characterization of the tumor immune microenvironment by immunohistochemistry and immunofluorescence on resected tumor tissue before and after MAC (see Section 12.2).

4.4 Safety endpoints

Adverse event will be further categorized as immune related adverse events (irAEs). Pre-defined stoppage criteria are outlined in Section 12.9, and pertain to the discontinuation of study regimen MPDL3280A prior to completion of 4 cycles. The completion of platinum based neoadjuvant chemotherapy, in the absence of the study drug, will be left to the provider's discretion. Delays in time to surgery will also be recorded.

4.5 Number of Patients

The study will accrue 30 evaluable patients as outlined in Section 14.

5. SUBJECT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

- Patients must have pathologically confirmed non-small cell lung cancer, including squamous, non-squamous, mixed histology, or large cell.
- Stage IB-IIIA
- Deemed potentially surgically resectable by a thoracic surgeon
  - If the FEV1 < 40%, surgical clearance must be obtained from a pulmonologist as well as a thoracic surgeon
- Age ≥ 18 years
- Radiologically measurable disease, as defined by RECIST v1.1
- Ability to understand and the willingness to sign a written informed consent document
- Females of child-bearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:
  - Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception (</=1% failure rate annually) without interruption, 28 days prior to starting therapy (including dose interruptions), and while on study medication or for a period of 90 days following treatment completion. *[Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*.
  - Have a negative serum pregnancy test (β -hCG) result at screening and agree to ongoing pregnancy testing during the course of the study, and after the end of study therapy. This applies even if the subject practices true abstinence from heterosexual contact.
- Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following treatment discontinuation, even if he has undergone a successful vasectomy.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Confirmed sufficient tissue and available block for analysis from a core biopsy-Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 10 unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression

Note: If any of the below requirements are not met, the patient may still be eligible if the tissue is deemed sufficient for analysis by the Sponsor-Investigator (written approval required).

- Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

- Patients who do not have tissue specimens meeting eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

- Adequate organ and marrow function as defined below:

– Lymphocyte count	≥300/mcL
– Neutrophil count	≥1,500/mcL
– Hemoglobin	≥9.0g/dl
– Platelets	≥100,000/mcL
– Total bilirubin	≤1.5 x institutional upper limit of normal (ULN) *Patients with Gilbert's disease: ≤3 x ULN
– AST(SGOT)/ALT(SGPT)	≤2.5 × ULN
– Alkaline phosphatase	≤2.5 x ULN
– INR and aPTT	≤ 1.5 × ULN *Unless the patient is on therapeutic anticoagulation
– Serum creatinine	≤1.5 x ULN OR
– Creatinine clearance	≥50 mL/min/1.73 m^2 by Cockcoft-Gault estimation

5.2 Exclusion Criteria

- Any approved anticancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 5 years prior to initiation of study treatment; however, the following are allowed:

  - Hormone-replacement therapy or oral contraceptives

  - Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)

- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with

expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score ≤ 6, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc.)

- Patients who are receiving any other investigational agents concurrently.
- Patients with no smoking history
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to MPDL3280A, carboplatin, or paclitaxel.
- Patients with active hepatitis B or C infections or a history of HIV infection.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection including TB, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- 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)

- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1

- Received IV antibiotics within 2 weeks prior to Cycle 1, Day 1. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible

- Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study

- Patients must not have >/= Grade 2 pre-existing peripheral neuropathy (per CTCAE)

- 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

- Pregnant women are excluded from this study because MPDL3280A, and other members of the immune checkpoint blocking class of agents, have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MPDL3280A, breastfeeding should be discontinued if the mother is treated with MPDL3280A.

- History of interstitial lung disease or pneumonitis of any cause

Immunotherapy-Related Exclusion Criteria:

- Prior treatment with anti–PD-1, anti-CTLA-4, or anti–PD-L1 therapeutic antibody or pathway-targeting agents

- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1

- Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	8	+	17	=	25
Ethnic Category: Total of all subjects	(10)	+	(20)	=	(30)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	1	+	3	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	9	+	17	=	26
Racial Category: Total of all subjects	(10)	+	(20)	=	(30)

5.4 Subject Recruitment

Patients will be recruited from the referral population within the investigator and co-investigators' clinical practices.

5.5 Early Withdrawal of Subjects

5.5.1 When and How to Withdraw Subjects

- If at any time the patient develops progressive disease, he/she will proceed directly to surgery as outlined in the study design.
- If at any time the patient develops unacceptable toxicity, he/she will be removed from study.
- If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (*i.e.*, a change in diagnosis), the patient will be removed from study.
- If the patient fails to comply with the defined treatment plan and follow-up evaluations, the patient will be removed from the study.
- If the patient withdraws consent for continued participation, he/she will be removed from study.
- If the study Sponsor or institutional review board (IRB)/independent ethics committee (IEC) terminate the study.
- In the event that a patient discontinues or is withdrawn from the study, the investigator will notify the Sponsor and perform all procedures indicated in the End of Study protocol.
- Patients withdrawn from the study for reasons other than toxicity or disease progression (e.g. protocol violation or withdrawal of consent) may be replaced at the discretion of the medical monitor and investigator.

5.5.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study, attempts will be made to obtain consent from the subject to record at least survival data up to the protocol-described end of subject follow-up period. In the event that a study subject is lost to follow-up, multiple methods of obtaining follow-up data will be utilized including weekly phone calls to the subject or next-of-kin, certified letters, and review of the institutional electronic medical record as well as public death certificate records. Subjects withdrawn because of unacceptable adverse events will be followed-until resolution or stabilization of the adverse event.

6. REGISTRATION PROCEDURES

6.1 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific

Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.304.6330 with the subject line "AAAQ3153 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

- Copy of pathology and surgical reports

- Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

- Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the protocol number followed by: "Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee at q3153@columbia.edu (CUMC's study specific Multicenter Core contact). The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email, with a request to register the patient "pending eligibility." The title of the email should read, "AAAQ3153 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request:

- Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (i.e. tissue, DNA, etc.) as applicable
- Redacted Signed HIPAA (or institutional equivalent)

- MCT CPDM Demographics Note to File form

The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (Multicenter Core contact) via telephone or email to communicate the following:

- Notify of pending registration request
- Confirm method of registration request submission (email or fax)
- Communicate expected time-line of registration request submission (i.e., same day, next day, within the hour, etc.)

To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee at q3153@columbia.edu:

- A signed Affiliate Site Eligibility Checklist (signed by the investigator)
- Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
  - Copy of required laboratory test and procedure reports (i.e., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
  - Copy of pathology and surgical reports
  - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

Please note: subject line of email or fax should include the following: "AAAQ3153 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7. SCHEDULE

7.1 Schedule of Assessments and Interventions

Procedure/Intervention[a]	***Every 3 week cycles (±2 days)***[k]							
	Pre-study	*C1D1*	*Repeated with each cycle*		*C2D1*	*C3D1*	*C4D1*	*Day of Surgery*
			C1D8	*C1D15*				
Informed consent	X							
Archived unstained slides[b]	X							
Clinical Assessments								
History and Physical Exam	X	X			X	X	X	
ECOG Performance Status	X	X			X	X	X	
Vital Signs	X	X	X	X	X	X	X	X
Concomitant Medications	X	X			X	X	X	
Adverse Events					X	X	X	
Treatment[c]								
MPDL3280A		X			X	X	X	
***nab*-paclitaxel**		X	X	X	X	X	X	
Carboplatin		X			X	X	X	
Tumor assessments								
Brain MRI	X							
CT Chest w/contrast	X					Pre-cycle		Pre-surgery
PET/CT (if applicable)	X							
Laboratory assessments[j]								
CBC	X	X	X	X	X	X	X	X[i]
Chemistry[d]	X	X	X	X	X	X	X	X[i]
PT/PTT	X	X			X	X	X	X[i]
TSH[e]	X				X	X	X	
Urinalysis	X							
Serum beta-HCG[f]	X	X						
EBV, HIV, HCV, HBV	X							
Research bloods[l]	X[g, h,]				X[h]	X[h]	X[h]	X[h, i]

a. Assessments should be performed prior to study drug infusion
b. At least 10 unstained slides are required. A repeat biopsy may be required if sufficient tissue is not available. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are NOT adequate for enrollment. Retrieval of archival tumor samples can occur outside the screening period.

c. For MPDL3280A, the initial dose will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes until loss of clinical benefit. For carboplatin + nab-paclitaxel, administer nab-paclitaxel over 30 minutes (-5/+10) followed immediately by carboplatin administered over 15−30 minutes. Administer nab-paclitaxel alone on Days 8 and 15.
d. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, uric acid
e. If TSH is abnormal, check T3 and free T4. If these are normal, include T3 and fT4 testing for subsequent cycles (including follow-up period)
f. Serum pregnancy test must be performed within 14 days prior to C1D1
g. At screening, research bloods will be drawn for a) germline sequencing as a companion to somatic tumor DNA sequencing , b) T-cell subsets, and c) HLA-typing (see lab manual)
h. PBMC isolation, serum and plasma (see lab manual)
i. To be collected pre-operatively (within 2 weeks of surgery)
j. Laboratory assessments to be done within 2 days prior to study drug infusion
k. Treatment is administered every 7 days (± 2 days) but treatments must be a minimum of 5 days apart.
l. Research Blood Samples are not to be collected on days when treatment is being delayed or held.

7.2 Follow-up Period

	Post-surgical follow-up date		
Assessment	*2-4 weeks*	*3 months (±3 weeks)*	*Survival*[c]
Clinical Assessments			
History and Physical	X	X	
ECOG PS	X		
Vital signs	X	X	
EKG			
Concomitant Meds	X[a]		
Adverse Events	X[b]		
Collection of Survival Status			X[c]
Laboratory Assessments			
CBC, Coag	X		
Chemistry	X		
TSH	X		
PBMC isolation, serum and plasma	X	X	
Imaging Assessments			
CT chest w/contrast		X	X

a. Only concomitant medications taken for ongoing adverse events related to study drug are recorded at this visit and they should continue to be recorded until resolution of the adverse event related to study drug.
b. Only adverse events related to the study drug are recorded at this visit and they should continue to be followed until resolution.
c. Survival visits are to occur every 4 to 6 months from the date of the 6 month Follow-up visit. Either in-person visits or telephone calls/email correspondence to assess the subject's status are acceptable.

7.3 Surgical resection processing

Resected tumor tissue will be processed for standard pathology evaluation and then remaining tumor tissue will be partitioned and processed in the following ways:

- Snap frozen in liquid nitrogen at -80 degrees Celsius for future DNA and RNA extraction.
- Processed in the Frattini lab as single-cell suspensions of tumor and infiltrating immune cells and then frozen at -80 degrees Celsius for future T-cell assays.
- Processed as formalin-fixed tissue and will be embedded in paraffin for future IHC assays.

Sufficient material must be collected to permit all planned correlative studies including (1) frozen material for DNA/RNA extraction, (2) FFPE material for IHC, and (3) digested cellular material for single-cell suspensions. Adjudication of sufficient material for (1) and (2) will be further certified by review of diff quik or H&E stained slide/touch prep from frozen and FFPE material to ensure tumor is present in collected material. Adequacy of material for single-cell suspensions will be determined by collection of at least 20 million live cells total.

8. TREATMENT PLAN

8.1 Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for MPDL3280A, nab-paclitaxel, and carboplatin are described in Section 10. Appropriate dose modifications for these agents are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Treatment is administered every 7 days (± 2 days) but treatments must be a minimum of 5 days apart.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
MPDL3280A	Steroids are	1200mg in	IV over 60	Day 1	3 weeks

	contra-indicated as premedications for cycle 1, but may be administered as anti-emetic prophylaxis at the clinicians judgement after C1	250cc NS	minutes on first administration, then over 30 minutes subsequently if tolerated		(21 days)
Nab-paclitaxel	Premedications to be administered per institutional guidelines	100 mg/m^2 reconstituted with 20cc NS	IV over 30 minutes.	Days 1, 8, 15	
Carboplatin	Premedications to be administered per institutional guidelines	AUC = 5 Diluted in 250mL NS	IV over 30 minutes, immediately after nab-paclitaxel	Day 1	

8.1.1 Investigational Agent

The dose level of MPDL3280A 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 on day 1 of every 3 weeks (21 [± 2] days). MPDL3280A 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 MPDL3280A and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of MPDL3280A 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 MPDL3280A 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 steroid premedication will be allowed for the first dose of MPDL3280A. 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:

1. 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.

2. 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.

3. 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 anaphylaxis precautions, standard institutional anaphylaxis procedures will be followed.

8.1.2 Nab-paclitaxel

ABRAXANE (nab-paclitaxel) is injected into a vein [intravenous (I.V.) infusion] over 30 minutes (-5/+10)). A dose of 100mg/m2 will be administered weekly (days 1, 8, and 15 of each cycle). The use of an in-line filter is not recommended. Following administration of nab-paclitaxel, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection, to ensure complete administration of the intended dose, according to local practice. No premedication is necessary for administration of this agent. This agent will be given second in sequence, after MPDL3280A and before carboplatin. Administration will begin after the post MPDL3280A infusion vital signs are collected.

8.1.3 Carboplatin

The dose of carboplatin will be calculated as an area under the curve (AUC) equal to 5, as calculated by the Calvert formula with GFR estimated by the Cockcroft-Gault formula. Carboplatin is infused over 30 minutes (+/- 15). Needles or IVs which contain aluminum will not be used in the preparation or administration of carboplatin. This medication will be premedicated per institutional guidelines. This agent will be administered after nab-paclitaxel infusion is completed.

Administration of carboplatin immediately after the completion of the ABRAXANE® infusion to patients with NSCLC did not cause clinically meaningful changes in paclitaxel exposure. The

observed mean AUCinf of free carboplatin was approximately 23% higher than the targeted value (6 min*mg/mL), but its mean half-life and clearance were consistent with those reported in the absence of paclitaxel.

8.1.4 Surgery

Standard surgical procedures and techniques, including but not limited to lobectomy, bilobectomy, pneumonectomy, and mediastinal lymph node dissection, will be determined by the surgical team in consultation with the investigator and will be based on CT scans obtained within 4 weeks prior to receiving study treatment. In the event of disease progression at the interim or post-treatment CT scans, surgical planning will be based on the updated imaging.

Surgical procedure should be scheduled approximately 4 weeks from last dose of study drug as best possible and at the clinical discretion of the treating physician and surgeon.

8.2 General Concomitant Medication and Supportive Care Guidelines

8.2.1 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.

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study regimen. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

Because there is a potential for interaction of nab-paclitaxel with other concomitantly administered drugs through the cytochrome P450 system (CYP2C8 and CYP3A4), the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

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 should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

8.2.2 Supportive Care

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 (for sites outside the United States, equivalent medications may be substituted per local 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

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with MPDL3280A 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 ≥ 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.

8.2.3 Excluded Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy

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.

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 MPDL3280A, 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 MPDL3280A. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with MPDL3280A 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 MPDL3280A.

8.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 4 cycles or until one of the following criteria applies:

- Disease progression

  - If the treating physician deems the patient has progressed clinically but does not meet RECIST criteria for PD, he/she should discuss with the surgeon and the principal investigator. The patient can be taken to the operating room sooner at the treatment team's discretion.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Protocol violation

In the event that a patient is discontinued on study treatment due to adverse events and is to proceed to the operating room sooner than was expected, the patient is to continue to present for study visits per study schedule during the interim. At each study visit, assessments per Table 7.1 are to be completed and documented as they would normally just without administration of study drug.

8.4 Duration of Follow Up

Patients will initially be followed by study team for 90 days after surgery or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, and will be contacted by phone at least every 1 month until 90 days after withdrawal to obtain data regarding long term outcomes.

Patients who complete the initial follow-up stage will then move into the Survival stage. Survival visits will occur every 4-6 months beginning at the end of the initial follow-up stage (90 days post-surgery). Survival can be assessed via in-person visits or telephone calls/email correspondence, until death, lost to follow-up, withdrawal of study consent, or for 3 years after date of surgery. Standard-of-care imaging is to be reviewed at each survival time point for evaluation of DFS.

8.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 8.5 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

Potential reasons for removal include adverse event, disease progression, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor or IRB/IEC.

9. DOSING DELAYS/DOSE MODIFICATIONS

9.1 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 v4.03. Patients will be assessed for safety (including laboratory values) at least every 7 days. Patients will be followed for safety for 90 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. All serious adverse events (SAEs) will be reported in an expedited fashion (see Section 10). In addition, the investigators will review and evaluate observed AEs on a regular basis. An continuous safety analysis will be conducted for treatment related adverse events.

Patients who have an ongoing 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.

Subjects are considered evaluable for assessment of treatment-related toxicity if they receive at least one dose of therapy. Grading of all toxicities will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

Immune-related adverse events (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Additional AEs that are not immune related may also be a potential safety event (see Section 12.7).

9.2 Management of Specific Safety Concerns with MPDL3280A

Toxicities associated or possibly associated with MPDL3280A 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-related adverse events (irAEs) 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 MPDL3280A may not have an immediate therapeutic effect and, in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with MPDL3280A; for higher-grade irAEs, MPDL3280A should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs may also mandate withholding MPDL3280A or the use of steroids. Assessment of the 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 MPDL3280A. MPDL3280A should be permanently discontinued in patients with life-threatening irAEs.

9.2.1 Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of MPDL3280A. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose ≤ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 1 provides a summary of dose modification guidelines for gastrointestinal toxicities.

Table 1 Dose Modification Guidelines for Gastrointestinal Toxicity

Toxicity	Description	Management
Diarrhea	Grade 2 (4–6 stools per day over baseline) < 5 days	Hold MPDL3280A, nab-paclitaxel, and carboplatin. Discontinue NSAIDS. Investigate for etiology. Restart MPDL3280A with chemotherapy once at baseline stool frequency.
	Grade 2 (4–6 stools per day over baseline) > 5 days	Hold MPDL3280A, nab-paclitaxel, and carboplatin. Discontinue NSAIDS. Consider a referral to a gastroenterologist. Administer anti-diarrheal agent (e.g., Imodium®). Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. Restart MPDL3280A once at baseline stool frequency.
	Abdominal pain Blood or mucus in stool OR Grade ≥ 3 (≥ 7 stools/day over baseline) with peritoneal signs, ileus, or fever	Hold MPDL3280A, nab-paclitaxel, and carboplatin. Discontinue NSAIDS. Rule out bowel perforation. Consider administering prednisone 60 mg/day or equivalent. Taper steroids over 1 month. Restart MPDL3280A if diarrhea is resolved and systemic steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue MPDL3280A for life-threatening, immune-related diarrhea or colitis.

NSAID = nonsteroidal anti-inflammatory drug.

9.2.2 Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of MPDL3280A.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti-nuclear

antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

Table 2 Dose Modification Guidelines for Hepatotoxicity

Toxicity	Description	Management
LFT abnormalities	AST/ALT (> ULN to 3 × ULN) with total bilirubin < 2 × ULN	Continue with the standard monitoring plan (i.e., LFTs every 3 weeks before dosing).
	AST/ALT (> 3 × ULN to < 10 × ULN) with total bilirubin < 2 × ULN	Continue MPDL3280A. Monitor LFTs at least weekly. Consider referral to a hepatologist.
	AST/ALT > 10 × ULN	Hold MPDL3280A. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by an oral prednisone (or equivalent) taper over 2–4 weeks. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart MPDL3280A if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue MPDL3280A for life-threatening, immune-related hepatic events.

Table 2 Dose Modification Guidelines for Hepatotoxicity (cont.)

Toxicity	Description	Management
LFT abnormalities (cont.)	AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	Hold MPDL3280A. Consult a hepatologist. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by oral taper over 1 month. If LFTs results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart MPDL3280A if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day.

IV = intravenous; LFT = liver function test; TNFα = tumor necrosis factor alpha; ULN = upper limit of normal.

9.2.3 Dermatologic Toxicity

Treatment-emergent rash has been associated with MPDL3280A. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 3.

Table 3 Dose Modification Guidelines for Dermatologic Toxicity

Toxicity	Description	Management
Dermatologic toxicity/rash (e.g., maculopapular or purpura)	Grade 1: Mild < 10% BSA	Continue MPDL3280A symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2: Moderate 10%–30% BSA	Continue MPDL3280A. Consider dermatologist referral. Administer topical steroids. Consider higher potency topical steroids if rash is unresolved.
	Grade 3: Severe > 30% BSA	Hold MPDL3280A. Consult dermatologist. Administer oral prednisone 10 mg or equivalent. If the rash is unresolved after 48–72 hours, administer oral prednisone 60 mg or equivalent. Restart MPDL3280A if rash is resolved and systemic dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue MPDL3280A for life-threatening, immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

9.2.4 Endocrine Toxicity

Hypothyroidism has been associated with the administration of MPDL3280A. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table .

Table 4 Dose Modification Guidelines for Endocrine Toxicity

Toxicity	Description	Management
Hypothyroidism	TSH elevated, asymptomatic	Continue MPDL3280A. Start thyroid-replacement hormone. Monitor TSH weekly.
	TSH elevated, symptomatic	Hold MPDL3280A. Consider referral to an endocrinologist. Restart MPDL3280A when symptoms are controlled by thyroid replacement and TSH levels are decreasing.

TSH = thyroid-stimulating hormone.

9.2.5 Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of MPDL3280A and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with MPDL3280A. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL_{CO}])

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Pulmonary toxicity should be managed according to the guidelines in Table 5.

Table 5 Dose Modification Guidelines for Pulmonary Toxicity

Toxicity	Description	Management
Pulmonary toxicity	GGO or non-infectious infiltrate in absence of hypoxia, or dyspnea	Hold treatment with MPDL3280A. Re-evaluate after 1 week. If no worsening in GGO/infiltrates and patient still asymptomatic, resume treatment with MPDL3280A. If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold MPDL3280A and refer for bronchoscopy. Consider starting low-dose oral prednisone 10 mg or equivalent. Re-evaluate after 1 week. Resume MPDL3280A if GGO/infiltrates improving.
	Hypoxia or dyspnea in presence of GGO or infiltrate without alternative etiology	Hold MPDL3280A. Consult a pulmonologist. Investigate for other etiologies and consider bronchoscopy. If bronchoscopy is consistent with immune-related etiology, start 60 mg prednisone equivalent per day followed by taper over 2 weeks. Restart MPDL3280A if symptomatically improved, infiltrates are resolved, and steroid use is ≤ 10 mg prednisone equivalent per day. Permanently discontinue MPDL3280A for life-threatening, immune-related pulmonary events.

GGO = ground glass opacities.

9.2.6 Pericardial and Pleural Effusions

Pericardial and pleural involvement with associated effusions is common in patients with cancer and has the theoretical potential to be exacerbated by inflammation associated with anti-tumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with pre-existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or

pleural effusions, appropriate workup includes cytology, LDH, glucose, cholesterol, protein concentrations (with pleural effusions), and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

9.2.7 Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

9.2.8 Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. MPDL3280A should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity should be managed according to the guidelines in Table 6.

Table 6 Dose Modification Guidelines for Eye Toxicity

Toxicity	Description	Management
Eye toxicity (autoimmune uveitis, iritis, or episcleritis)	Symptomatic	Hold MPDL3280A. Consult ophthalmologist and start topical corticosteroid eye drops. MPDL3280A may be restarted following resolution of the events. Permanently discontinue MPDL3280A for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

9.3 Carboplatin and nab-paclitaxel

Dose reductions, holds, and discontinuations for each study drug may be made as outlined below and in the respective Package Inserts or according to physician judgment. When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the regimen, all study drugs should generally be held and resumed together to remain synchronized. However, if it is anticipated that chemotherapy will be delayed by 2 weeks or more, then MPDL3280A should be given without the chemotherapy if there is no contraindication; this should be discussed with the Medical Monitor prior to re-initiating therapy. Investigators should be vigilant and alert to early and overt signs of myelosuppression/infection/febrile neutropenia so

that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity. Dose modifications of carboplatin and nab-paclitaxel are allowed as described in the following sections: hematologic, gastrointestinal, neurologic, hepatic, and other toxicities.

If a patient experiences adverse events and there are conflicting recommendations, the investigator will use the recommended dose adjustment that reduces the dose to the lowest level. All adverse events should first be screened for potential immunogenic etiologies induced by MPDL3280A, as outlined in 9.2.

9.3.1 Hematologic Toxicity

ANC must be ≥ 1500/mm3 and platelet counts must be ≥ 100,000/mm3 on Day 1 of each cycle. Nab-paclitaxel should not be administered on Days 8 or 15 of the cycle until counts recover to an ANC ≥ 1500/mm3 and platelets ≥ 50,000 cells/mm3. If nab-paclitaxel cannot be administered on Day 8 or 15 of the cycle, this treatment can be skipped, and the next dose should be given per original treatment schedule as long as counts have recovered to permissible levels. However, if ANC and platelets are too low for Day 1 administration, then Day 1 treatment should be postponed until count recovery. When dosing resumes, the carboplatin and nab-paclitaxel doses should be permanently reduced as outlined in Table 7. Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

Table 7: Permanent Dose Reductions for Toxicities and Dosing on the Study

Adverse Drug Reaction	**Occurrence**	***nab*-Paclitaxel Dose (mg/m^2)**	**Carboplatin Dose (AUC mg*min/mL)**
Neutropenic Fever (ANC < 500/mm^3 with fever > 38°C) OR Delay of next cycle by ≥ 7 days for ANC < 1500/mm^3 OR ANC < 500/mm^3 for ≥ 7 days	First	75	4.0
	Second	50	3.0
	Third	Discontinue Treatment*	
Platelet count < 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment*	
Sensory Neuropathy Grade 3 or 4	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment*	
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea	First	75	4.5
	Second	50	3.0

Grade 3 mucositis Any other Grade 3 or 4 nonhematologic toxicity	Third	Discontinue Treatment*
Grade 4 cutaneous toxicity, diarrhea or mucositis	First	Discontinue Treatment*

ANC = Absolute Neutrophil Count; AUC = area under the curve.
* If an adverse event that requires dose reduction recurs after the dose has been reduced twice, the subject should generally have treatment discontinued unless, at the discretion of the investigator, there is evidence of continuing benefit to the subject that outweighs the risk of recurrent toxicity. Re-Escalation is not permitted at anytime.

9.3.2 Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 8 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 8: Carboplatin and Nab-Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity		**Next Dose for Carboplatin as % of previous dose***	**Next Dose for nab-paclitaxel as % of previous dose***
Diarrhea	Grade 3 or 4**	75%	75%
Oral Stomatitis/Mucositis	Grade 3 or 4	75%	75%
Nausea/Vomiting	Grade 3 or 4	75%	75%
*If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC. ** As per investigator discretion AUC = area under the curve (mg x min / mL)			

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs in spite of anti-emetics, the dose should be reduced by 25% for the next course. If tolerated, the dose should be increased back to 100% as soon as possible.

If, on Day 1 of any treatment cycle, the patient has oral mucositis/stomatitis, the treatment should be withheld until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 3 weeks, the patient's chemotherapy will be discontinued. If acute Grade 3 oral mucositis occurs at any time, a 75% dose should be given when the oral mucositis is completely cleared. This is a permanent dose reduction.

9.3.3 Neurological Toxicity (Nab-Paclitaxel Only)

Nab-paclitaxel should be withheld for Grade 3-4 peripheral neuropathy. Nab-paclitaxel and carboplatin may be resumed at reduced doses (see table below) when peripheral neuropathy recovers to Grade 1 or completely resolves.

Table 9: Nab-Paclitaxel and Carboplatin Permanent Dose Reductions for Neurological Toxicity

Toxicity	Occurrence	Next Dose for Carboplatin	Next Dose for nab-paclitaxel
Grade 3 or 4 sensory neuropathy	First	Decrease to 4.5 AUC	Decrease to 75mg/m^2
	Second	Decrease to 3 AUC	Decrease to 50mg/m^2
	Third	Discontinue treatment	
AUC = area under the curve (mg x min / mL)			

9.3.4 Hepatic Toxicity (Nab-Paclitaxel Only)

For patients who develop Grade ≥ 3 hepatotoxicity during study treatment (ALT and/or AST ≥ 5 x ULN or total bilirubin ≥ 3 x ULN), study treatment should be interrupted. Hepatic toxicity must resolve to Grade ≤ 1 prior to dosing. If nab-paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when the nab-paclitaxel is resumed. If nab-paclitaxel is withheld, hepatic values must recover to Grade ≤ 1 within 3 weeks or the patient's nab-paclitaxel treatment will be discontinued. No dose reductions for carboplatin will be made for hepatic toxicity.

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/m2). Nab-paclitaxel will be discontinued for Grade 4 hepatic toxicity.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement. All study medication should be discontinued if the disease under investigation has progressed.

9.3.5 Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, carboplatin or nab-paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment should then be resumed at 75% dose (permanent dose reduction) for Grade 3 toxicities and 50% of dose (permanent dose reduction) for Grade 4 toxicities. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no

dose reduction should be made. For guidelines on the dosing of other study drugs when carboplatin or nab-paclitaxel are held, see Section 5.1.5.

9.4 Potential Overlapping Toxicities

The risk of overlapping toxicities between MPDL3280A, carboplatin, and nab-paclitaxel is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of MPDL3280A.
Toxicities should initially be managed according to the recommendations above, with dose holds and modifications (if applicable) applied to the component of the study regimen judged to be the primary cause. For severe (Grade 3) or persistent Grade 1/2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, MPDL3280A is a potential inciting factor, the dose of MPDL3280A may be held indefinitely. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse events

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

10.2 Definitions

Adverse Event:

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 subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with lung cancer 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.
- Preexisting 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.

Serious Adverse Event:

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a

seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 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. For this study, the study treatment follow-up is defined as 90 days following surgical resection procedure, or 90 days following the decision to remove the subject from study treatment, whichever is earliest.

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved treatment-related adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.
Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.3 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, 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 MPDL3280A, 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 the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study regimen or dose reduction and, if applicable, reappears upon re-challenge.

No

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

10.4 Eliciting of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

10.5 Specific Instructions for Recording Adverse Events

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

10.5.1 Diagnosis vs. 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.

10.5.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), 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".

10.5.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting 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 preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.5.4 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 subject 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 subject 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 preexisting 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.

10.5.5 Pregnancy

If a female subject becomes pregnant while receiving the study drug or within the follow-up period (for female patients within one year after the last dose of MPDL3280A or the partner of a male patient within three months of completing therapy), a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the 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 regimen should be reported as an SAE.

10.5.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior MPDL3280A exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

10.5.7 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech, Celgene, and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly (no less frequently than monthly) line listings of cases received by the other party.

If discrepancies are identified with regards to cases reported to Genentech, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents for Genentech within the 'Activation Package'.

10.5.8 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

The MPDL3280A Events of Special Interest are:

- Pneumonitis
- Colitis
- Endocrinopathies: Diabetes mellitus, Pancreatitis, Hyperthyroidism, or Adrenal Insufficiency
- Hepatitis
- Transaminitis: Grade ≥2 (AST or ALT >3x ULN and bilirubin >2x ULN) *OR* AST/ALT >10x ULN
- Systemic Lupus Erythematosus
- Guillain Barre Syndrome, Myasthenia gravis

- Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza like illness, systemic inflammatory response syndrome (SIRS), systemic inflammatory activation (SIA), or infusion reaction syndromes
- Suspected Transmission of an Infectious Agent (STIAMP) by the study drug

  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.

10.6 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at : http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For multi-site trials such as this study where a Columbia University Medical Center investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor as described below.

In addition to the reporting requirements for SAEs, a separate case report form will be made for reporting of any grade adverse events attributable to research biopsies. These events will not require expedited reporting unless they also meet the requirements for SAE reporting, as detailed below.

Copies of all IND safety reports submitted to the FDA and/or institutional IRB by the institution under the institution's IND will be shared with an Acetylon representative so that these reports can be evaluated and included in the Investigator Brochure and future Acetylon IND safety submissions per regulations.

10.7 Reporting of Adverse Events

10.7.1 IRB Notification by Sponsor-Investigator

Reports of all Serious events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.7.2 Reporting to Drug Manufacturer by Sponsor-Investigator

10.7.2.1 Investigator Reporting to Genentech

Investigators must report all SAEs to Genentech Safety within the timelines described below. The completed MedWatch/case report/equivalent should be submitted immediately upon completion via fax to Genentech Drug Safety at:

Fax: 650-238-6067

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

SAE reports and AEs of Special Interest, whether related or unrelated to MPDL3280A, will be transmitted to Genentech within 24 hours of the Awareness Date.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the MPDL3280A and within the follow-up period (for female patients within one year after the last dose of MPDL3280A or the partner of a male patient within three months of completing therapy) will be transmitted to Genentech Drug Safety within 24 hours of the Awareness Date.
- All non-serious MPDL3280A AEs originating from the study will be forwarded Genentech quarterly.

In addition to SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- 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

MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and submitting it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally Genentech / Roche may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech / Roche Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

10.7.2.2 Expedited Investigator Reporting to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to ABRAXANE® based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form or equivalent of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-NSCLC-PI-005652 and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

Overdose

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of carboplatin, nab-paclitaxel, or MPDL3280A assigned to a given patient, regardless of any associated adverse events or sequelae.

IV 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

10.8 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator 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.

10.9 Additional Reporting Requirements for IND (MPDL3280A)

The sponsor is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), Celgene, and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

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 IND sponsor is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the IND sponsor to be possibly related to the use of MPDL3280A. An unexpected AE is one that is not already described in the MPDL3280A 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 IND sponsor 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 MPDL3280A. An unexpected AE is one that is not already described in the MPDL3280A 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 3500A 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 submitted to the following:

Genentech Drug Safety:

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

Site's IRB:

Columbia University Medical Center IRB
154 Haven Avenue, 1st Floor New York, NY 10032
Ph 212-305-5883
Fax 212-305-1316
Email irboffice@columbia.edu

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

Tel: (888) 835-2555

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

IND Annual Reports

Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be submitted to Genentech Drug Safety:

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

10.9.1 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites. CUMC will notify the HICCC DSMC within 24 hours of knowledge of the SAE once informed by the affiliate site.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

11. PHARMACEUTICAL INFORMATION

Study Drugs

11.1 Description

MPDL3280A 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. MPDL3280A 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. MPDL3280A targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). MPDL3280A also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells. It is administered as an intravenous formulation.

nab-Paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as "Celgene"], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with a mean particle size of approximately 130 nanometers. *nab*-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because *nab*-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur.[63-65] *nab*-Paclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in *nab*-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m2 for *nab*-paclitaxel (Study DM97-123) versus 175 mg/m2 for Taxol.[66] The use of albumin-bound paclitaxel also enables *nab*-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, *nab*-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries/regions as a new product, rather than as a generic formulation of Taxol.

For further details of pharmacokinetics, absorption, and excretion of drugs, please refer to manufacturer insert.

11.2 Treatment Regimen

Four (4) cycles of 21 days each will be administered as follows:

- MPDL3280A fixed dose of 1200 mg IV on day 1 of every 21 days
- Nab-paclitaxel 100 mg/m^2 IV on days 1, 8 and 15
- Carboplatin AUC = 5 IV on day 1

11.3 Method for Assigning Subjects to Treatment Groups

All patients enrolled in this study will receive the same study treatment protocol.

11.4 Preparation and Administration of Study Drug

Carboplatin and nab-paclitaxel are prepared according to the recommendations from the manufacturers' label. Carboplatin is obtained through standard commercial pharmacies. Nab-paclitaxel is supplied by Celgene. MPDL3280A is supplied by Genentech.

11.4.1 Nab-paclitaxel (ABRAXANE®)

ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is paclitaxel formulated as albumin-bound nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. ABRAXANE® is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion.

nab-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent-related HSRs (Taxol US prescribing information). Cremophor EL has been shown to leach plasticizers, specifically di(2-ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing.[67-72] Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (eg, carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (eg, those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel.[63,66]

ABRAXANE® is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line filter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

11.4.2 Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of nab-paclitaxel administration, over 15–30 minutes to achieve an initial target AUC of 6 mg/mL/min (Calvert formula dosing) and with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] +25)

NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CrCl). The CrCl is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age})\ (\text{wt})}{72 \times \text{Scr}} \quad (\times 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min age= patient's age in years wt = patient's weight in kg Scr = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate GFR using a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.
If a patient's GFR is estimated based on serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg •min/mL) × (GFR+ 25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC= 6, the maximum dose is 6 × 150 = 900 mg.
For a target AUC= 5, the maximum dose is 5 × 150 = 750 mg.
For a target AUC= 4, the maximum dose is 4 × 150 = 600 mg.

Refer to the FDA's communication regarding carboplatin dosing using the following URL for more details:
http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm228974.htm.

11.4.3 MPDL3280A (Atezolizumab)

The MPDL3280A 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 MPDL3280A solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The MPDL3280A drug product is formulated as 60 mg/mL MPDL3280A in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

MPDL3280A must be refrigerated at 2°C – 8°C (36°F – 46°F) upon receipt until use. MPDL3280A vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the MPDL3280A 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 MPDL3280A Investigator's Brochure.

The dose level of MPDL3280A 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). MPDL3280A 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 MPDL3280A and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of MPDL3280A 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 MPDL3280A 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 steroid premedication will be allowed for the first dose of MPDL3280A. 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.

11.5 Subject Compliance Monitoring

Compliance will be monitored by office visit documentation.

11.6 Prior and Concomitant Therapy

All history pertaining to prior and/or concomitant medical therapy will be collected at the time of study enrollment.

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 (for sites outside the United States, equivalent medications may be substituted per local 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).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with MPDL3280A 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 ≥ 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 should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

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

chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy. 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) should be discontinued during the study; this agent could potentially alter the activity and the safety of MPDL3280A. Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

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 MPDL3280A, 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 MPDL3280A. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with MPDL3280A but may be administered at the discretion of the treating physician. This includes the administration of rescue therapies for treatment related toxicity. 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 MPDL3280A.

Concomitant use of yellow fever vaccine is contraindicated in subjects receiving carboplatin. Subjects receiving carboplatin must not receive Yellow Fever vaccine.

11.7 Packaging

As per sponsor packaging instructions.

11.8 Blinding of Study Drug

This drug is not blinded.

11.9 Receiving, Storage, Dispensing and Return

11.9.1 Receipt of Drug Supplies

The study drug MPDL3280A will be shipped to the investigative site by Genentech, and will be stored and prepared within the investigational pharmacy.

ABRAXANE® will be supplied by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number, product name, dosage form and strength, medication identification/kit number,

lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form as well as the Drug Accountability Log to Celgene Corporation at 908-673-2779.
Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff must count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

11.9.2 Storage

Storage conditions are described in the MPDL3280A Investigators' Brochure as well as the Manufacturer's Package Insert for carboplatin and nab-paclitaxel.

11.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug administration. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

11.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of the study drug. Remaining study drug will be returned to the Sponsor.

12. OUTCOME MEASUREMENTS

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Patients do not need labs repeated prior to treatment on C1D1 unless there is a change in clinical status. Scans and x-rays must be done $\leq$4 weeks prior to the start of therapy.

12.1 Pathologic Response Rate

The primary outcome of interest in this study is the rate of major pathologic response. All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories for the primary outcome:

1) complete pathologic response: no pathologically detectable viable tumor
2) major pathologic response: <10% residual viable tumor (see diagram below)
3) partial pathologic response: ≤50% residual viable tumor
4) inadequate response: >50% residual viable tumor
5) early death from malignant disease
6) early death from toxicity
7) unknown (not assessable, insufficient data)

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-7 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

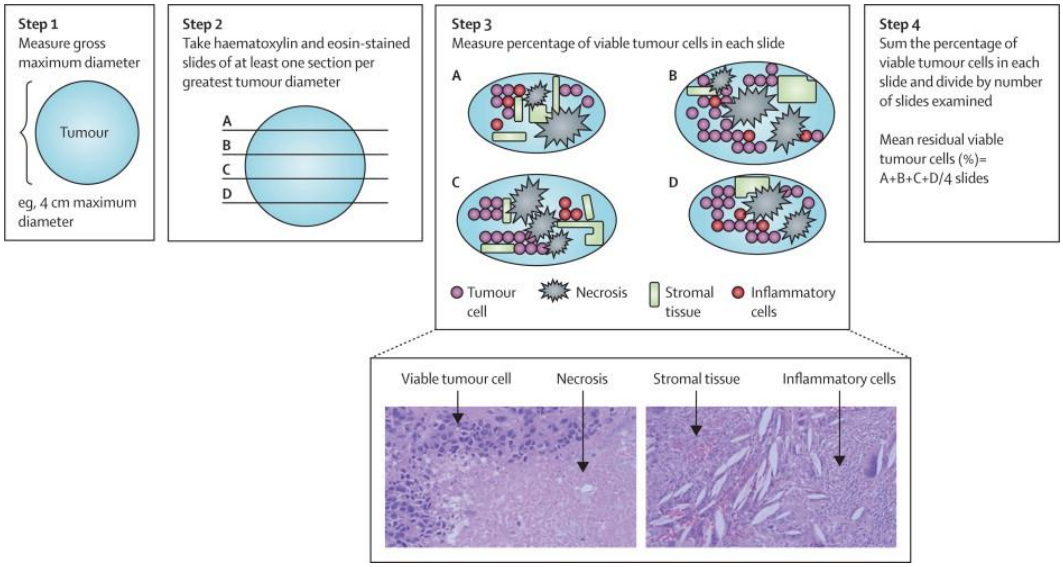


Diagram 1 Quantifying Pathologic Response

Methods for quantifying pathologic response have been previously described (Hellmann 2014). Pathologic response will be calculated as the percentage of viable tumor within a tumor cross section, and then averaged across multiple tumor cross sections.

12.2 Tumor Immune Microenvironment

The balance of stimulatory and inhibitory checkpoints that determine T-cell activation or inhibition will be evaluated by immunohistochemistry/immunofluorescence on tumor tissue to evaluate for the presence of PD-1 and PD-L1, PD-L2 on tumor cells, presence of co-stimulatory

(OX40, ICOS, CD137) and co-inhibitory (CTLA4, LAG3, TIM3) markers on pre-treatment tissue and post-treatment specimen.

Immunohistochemistry/immunofluorescence will be performed to assess for co-localization of CD3+ and CD8+ TILs in pre-treatment biopsies and post treatment resection samples and/or PBMCs, serum and plasma. Slides will be stained for CD3 and CD8 and undergo automated quantification. In addition surgical samples from tumor resection will be used to create single cell suspensions, which will be used for tumor separation and isolation of tumor-infiltrating lymphocytes (TILs); tumor and immune cells will be analyzed using multiparametric flow cytometry (CD3, CD4, CD8, FoxP3, Ki67, ICOS, PD-1, LAG-3, TIM-3, and CTLA-4).treat

12.3 Exploratory Biomarkers of Response

An exploratory objective of this study is to identify potential biomarkers of response to the study treatment. Such blood and tissue biomarkers may provide evidence for the biological activity of MPDL3280A, and may inform selection of patients most likely to benefit from treatment with MPDL3280A.

Biomarker analysis may include, but is not limited to, blood based markers such as peripheral blood lymphocyte neoantigen activity, pre- and post-treatment tissue flow cytometry, tissue immune signature as detected by Nanostring microarray, tumor whole exome sequencing and total mutational and neoantigen burden. See Table 10.

Table 10: Methods

Tumor	
Non-synonymous mutation burden	Exome and RNAseq analysis [73-83]
Mutational smoking signature	Exome and RNAseq analysis [73-83]
Neoantigen prediction	In silico neoantigen prediction [45]
MHC, PD-L1, PD-L2, LAG3, IDO, Tim3, Ki-67	IHC/IF [84]
CD3, CD4, CD8, PD-1, FOXP3, TIA-1	IHC/IF [84]
PBMCs, serum and plasma	
Neoantigen validation in vitro (quantitative)	Intracellular cytokine staining [85]
Neoantigen validation in vitro (qualitiative)	Multimer assays [46]
Tumor and PBMCs, serum and plasma	
T cell receptor clonality	TCR sequencing [86]
Blood	
Germline sequencing	Exome analysis [73-83]
HLA typing	HLA sequence-based typing [87]

12.4 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for

nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.5 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy/Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology/Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or

scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.6 Radiologic Response Criteria

12.6.1 Radiologic Response Rate

In addition to a baseline scan, scans should be obtained after cycle 2 (not less than 5 weeks after initiation of treatment) and after cycle 4.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions:

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with MAC.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.6.2 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions,

taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Responder: For this study, a patient will be defined as a responder if they exhibit disease control (having shown CR, PR or SD radiographically) after receiving the first 2 cycles of treatment.

Non-Responder: For this study, a patient will be defined as a non-responder if they show PD as their best response following the first 2 cycles of treatment.

12.6.3 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.7 Disease-Free Survival

DFS is defined as the duration of time from date of surgery to time of recurrence or death, whichever occurs first.

12.8 Response Review

Not applicable.

12.9 Safety Stopping Rules

The study may be discontinued if the study is terminated by the data and safety monitoring committee, the Food and Drug Administration (FDA), or other regulatory authorities.

Any unforeseen deaths or serious adverse events may, after a discussion between the principal investigator and investigators at other sites, prompt an interruption to study accrual pending a full investigation into the circumstances surrounding the event.

Early safety stopping rules will be defined as a 10% rate of occurrence of qualifying safety events or those which prohibit or delay surgical intervention. Therefore, if at any time ≥ 3 of 30 patients experience a safety event that prohibits surgery or delays medical operability more than 37 days beyond the preplanned surgical date (day 0), the regimen will be deemed unsafe, and the study stopped.

Subjects are considered evaluable for assessment of treatment related toxicity if they receive at least one dose of therapy. Grading of all toxicities will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

A toxicity defined as a safety event for this study will be any Grade 3 or higher of the following:

- Any ≥ Grade 3 colitis
- Any Grade 4 immune-related AE (irAE)
- Any Grade 3 irAE that does not downgrade to ≤ Grade 2 within 1 week after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation higher than 8 × upper limit of normal (ULN) or total bilirubin higher than 5 × ULN
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.
- Additional AES that are not immune related may also be a potential safety event including any grade 3 or higher toxicities that do not downgrade to ≤ Grade 2 within 1 week after onset of the event despite maximal supportive care or downgrade to ≤ Grade 1 or baseline within 14 days

The definition excludes the following conditions:

- Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic or minimally symptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of disease, lymph nodes, etc)
- Dosing may continue despite concurrent vitiligo and alopecia of any grade

13. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.2.

13.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

13.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

13.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

13.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source

documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

13.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

13.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

13.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

13.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.
If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);
Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

13.9 Ethical Considerations

Compliance with Laws and Regulations

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive MPDL3280A treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 8.5.

Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.
Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.
Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech and Celgene representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

A two-stage design will be used to evaluate the neoadjuvant combination of MPDL3280A + nab-paclitaxel and carboplatin (MAC) in patients with resectable stage IB, II and IIIA NSCLC. The primary goal is to determine whether the rate of major pathologic response (MPR, < 10% residual viable tumor cells at surgery) may be increased from 22% to 44% by adding chemotherapy to an anti-PD-L1 antibody alone. Initially, 18 patients will be enrolled in the first stage and treated with the study drug combination. Protocol accrual will be terminated after the first stage if only 4 or fewer patients were to achieve MPR at surgery.

Otherwise, the protocol will proceed to the second stage for a total of 30 patients. If the overall number of MPR were 11 or more, the study drug combination will be considered to have improved neoadjuvant efficacy. The two-stage design provides 83% power for detecting an MPR rate of 44% under the alternative hypothesis. If the underlying rate were truly only 22%, the probability of early termination at the first stage is 64% while the overall rate of a false positive trial is 5% (alpha level).

As the trial will be the first time chemotherapy and an anti-PD-L1 antibody will be administered

together preoperatively in NSCLC patients, safety will be monitored on a continual basis. The protocol will be stopped early as soon as 3 patients were to experience serious or prolonged treatment related and immune-related adverse events as defined in section 12.9, as well as extended treatment related delay to surgery defined as >37 days from preplanned Day 0 (>30 days from preplanned day 0 plus 7 extra days to allow for OR scheduling and other clinical constraints). The probability of observing treatment related safety events in 3 or more out of 30 patients is 85% if the true rate were 15%. In contrast, the probability is only 19% if the underlying rate were 5% in the protocol population.

The association between MPR response and post-treatment IHC values will be further explored using logistic regression after adjusting for pre-treatment IHC values. In addition, the differences between MPR responders and MPR non-responders with respect to IHC post-treatment values adjusted for baseline IHC values will be assessed using an analysis of covariance model or a rank based analysis of covariance model.

14.2 Size/Accrual Rate

A total sample size of 30 evaluable patients will be accrued in the first and second stages, with a projected accrual rate of 2 patients per month per site.

14.3 Analysis of Secondary Endpoints

Adverse events will be scored according to NCI CTCAE v4.03, and their frequency and nature will be tabulated by categories. The rates of adverse events, pathologic response and objective response (RECIST v1.1) will be reported with 95% confidence intervals based on the exact binomial distribution. DFS and OS will be estimated using the Kaplan-Meier method. Markers of immune reactivity measured in lung tumor specimens, draining lymph nodes, and peripheral blood will be evaluated pre- and post-treatment. Baseline levels and post-treatment changes will be summarized using descriptive statistics and graphical methods.

14.4 Reporting and Exclusions

14.4.1 Evaluation of toxicity

All patients will be evaluable for toxicity if they have received at least one dose of protocol therapy.

14.4.2 Evaluation of response

Patients will be evaluable for objective response if they have received at least one cycle of protocol therapy and undergone response assessment or if they exhibit objective progression prior to the end of cycle 1. All patients will be evaluated for pathologic response status according to section 12.1 whether they undergo resection or not.

15. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

16. STUDY FINANCES

16.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

16.2 Subject Stipends or Payments

No stipend.

17. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. The study drug manufacturers reserve the right to review all manuscripts prior to submission for publication.

18. REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
3. Howlader N, Noone AM, Krapcho M. SEER Cancer Statistics Review, 1975-2011. National Cancer Institute Bethesda, MD, http://seercancergov/csr/1975_2011/ 2014;based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
4. Langer CJ, Besse B, Gualberto A, Brambilla E, Soria JC. The evolving role of histology in the management of advanced non-small-cell lung cancer. J Clin Oncol 2010;28:5311-20.
5. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.
6. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
7. Group NM-aC, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
8. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
9. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 2007;369:1929-37.
10. Pisters KM, Kris MG, Gralla RJ, Zaman MB, Heelan RT, Martini N. Pathologic complete response in advanced non-small-cell lung cancer following preoperative chemotherapy: implications for the design of future non-small-cell lung cancer combined modality trials. J Clin Oncol 1993;11:1757-62.
11. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012;30:172-8.
12. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
13. Martini N, Kris MG, Gralla RJ, et al. The effects of preoperative chemotherapy on the resectability of non-small cell lung carcinoma with mediastinal lymph node metastases (N2 M0). Ann Thorac Surg 1988;45:370-9.
14. Martini N, Kris MG, Flehinger BJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan-Kettering experience with 136 patients. Ann Thorac Surg 1993;55:1365-73; discussion 73-4.
15. Kris MG, Pisters KM, Ginsberg RJ, et al. Effectiveness and toxicity of preoperative therapy in stage IIIA non-small cell lung cancer including the Memorial Sloan-Kettering experience with induction MVP in patients with bulky mediastinal lymph node metastases (Clinical N2). Lung Cancer 1995;12 Suppl 1:S47-57.

16. Ng KK, Kris MG, Ginsberg RJ, et al. Induction chemotherapy employing dose-intense cisplatin with mitomycin and vinblastine (MVP400), followed by thoracic surgery or irradiation, for patients with stage III nonsmall cell lung carcinoma. Cancer 1999;86:1189-97.
17. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002;20:247-53.
18. Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol 2009;4:1380-8.
19. Pisters KM, Ginsberg RJ, Giroux DJ, et al. Induction chemotherapy before surgery for early-stage lung cancer: A novel approach. Bimodality Lung Oncology Team. J Thorac Cardiovasc Surg 2000;119:429-39.
20. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.
21. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465-71.
22. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012;307:1383-93.
23. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005;23:8664-70.
24. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
25. Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol 2006;24:1037-44.
26. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol 1999;17:460-9.
27. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019-27.
28. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19:4224-37.
29. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001:96-102.

30. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-85.
31. Pataer A, Kalhor N, Correa AM, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 2012;7:825-32.
32. Hellmann MD, Chaft JE, William WN, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. The Lancet Oncology 2014;15:e42-e50.
33. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752-9.
34. Chaft JE, Rusch V, Ginsberg MS, et al. Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. J Thorac Oncol 2013;8:1084-90.
35. Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. Clin Cancer Res 2010;16:2861-71.
36. Hellmann MD, Chaft JE, William WN, Jr., et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. The lancet oncology 2014;15:e42-50.
37. Junker K, Thomas M, Schulmann K, Klinke F, Bosse U, Muller KM. Tumour regression in non-small-cell lung cancer following neoadjuvant therapy. Histological assessment. J Cancer Res Clin Oncol 1997;123:469-77.
38. Mouillet G, Monnet E, Milleron B, et al. Pathologic complete response to preoperative chemotherapy predicts cure in early-stage non-small-cell lung cancer: combined analysis of two IFCT randomized trials. J Thorac Oncol 2012;7:841-9.
39. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol 2001;22:265-8.
40. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.
41. Carter L, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. Eur J Immunol 2002;32:634-43.
42. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.
43. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.
44. Azuma T, Yao S, Zhu G, Flies AS, Flies SJ, Chen L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood 2008;111:3635-43.
45. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to

CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
46. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
47. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2015;33:2004-12.
48. Rizvi NA, Garon EB, Patnaik A, et al. Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2014;31:8007.
49. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.
50. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.
51. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257-65.
52. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522-30.
53. Tarhini AA, Edington H, Butterfield LH, et al. Immune monitoring of the circulation and the tumor microenvironment in patients with regionally advanced melanoma receiving neoadjuvant ipilimumab. PLoS One 2014;9:e87705.
54. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.
55. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Final Results of a Phase III Trial. Journal of Clinical Oncology 2012;30:2055-62.
56. Ahmed S, Birnbaum AE, Safran HP, et al. Pathologic response after neoadjuvant carboplatin and weekly paclitaxel for early-stage lung cancer: a Brown University oncology group phase II study. J Thorac Oncol 2011;6:1432-4.
57. Merritt RE, Mahtabifard A, Yamada RE, Crystal RG, Korst RJ. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609-17.
58. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050-9.
59. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res 2015;3:436-43.
60. Antonia S, Brahmer JR, Gettinger SN, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2014;32:suppl; abstr 8113.
61. Liu S, Powderly JD, Camidge DR. Safety and efficacy of MPDL3280A in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell

lung cancer. J Clin Oncol 2015;33:abstr 8030.
62. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
63. Ibrahim NK, Desai N, Legha S, et al. Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res 2002;8:1038-44.
64. Sparreboom A, van Zuylen L, Brouwer E, et al. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. Cancer Res 1999;59:1454-7.
65. ten Tije AJ, Verweij J, Loos WJ, Sparreboom A. Pharmacological effects of formulation vehicles : implications for cancer chemotherapy. Clin Pharmacokinet 2003;42:665-85.
66. Nyman DW, Campbell KJ, Hersh E, et al. Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. J Clin Oncol 2005;23:7785-93.
67. Allwood MC, Martin H. The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection. Int J Pharm 1996;127:65-71.
68. Gelderblom H, Verweij J, Nooter K, Sparreboom A. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 2001;37:1590-8.
69. Venkataramanan R, Burckart GJ, Ptachcinski RJ, et al. Leaching of diethylhexyl phthalate from polyvinyl chloride bags into intravenous cyclosporine solution. Am J Hosp Pharm 1986;43:2800-2.
70. Song D, Hsu LF, Au JL. Binding of taxol to plastic and glass containers and protein under in vitro conditions. J Pharm Sci 1996;85:29-31.
71. Xu QA, Trissel LA, Zhang Y. Paclitaxel Compatibility with the IV Express Filter Unit. Int J Pharm Compd 1998;2:243-5.
72. Pfeifer RW, Hale KN, Cronquist SE, Daniels M. Precipitation of paclitaxel during infusion by pump. Am J Hosp Pharm 1993;50:2518, 21.
73. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 2009;25:1754-60.
74. DePristo MA, Banks E, Poplin R, et al. A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nature genetics 2011;43:491-8.
75. De Baets G, Van Durme J, Reumers J, et al. SNPeffect 4.0: on-line prediction of molecular and structural effects of protein-coding variants. Nucleic acids research 2012;40:D935-9.
76. Larson DE, Harris CC, Chen K, et al. SomaticSniper: identification of somatic point mutations in whole genome sequencing data. Bioinformatics 2012;28:311-7.
77. Koboldt DC, Zhang Q, Larson DE, et al. VarScan 2: somatic mutation and copy number alteration discovery in cancer by exome sequencing. Genome Res 2012;22:568-76.
78. Cibulskis K, Lawrence MS, Carter SL, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nature biotechnology 2013;31:213-9.
79. Robinson JT, Thorvaldsdottir H, Winckler W, et al. Integrative genomics viewer. Nature biotechnology 2011;29:24-6.
80. Sherry ST, Ward M, Sirotkin K. dbSNP-database for single nucleotide

polymorphisms and other classes of minor genetic variation. Genome Res 1999;9:677-9.
81. NHLBI GO Exome Sequencing Project (ESP).http://evs.qs.washington.edu/EVS Exome Variant Server.
82. Via M, Gignoux C, Burchard EG. The 1000 Genomes Project: new opportunities for research and social challenges. Genome medicine 2010;2:3.
83. Liu X, Jian X, Boerwinkle E. dbNSFP v2.0: a database of human non-synonymous SNVs and their functional predictions and annotations. Human mutation 2013;34:E2393-402.
84. Taube JM, Young GD, McMiller TL, et al. Differential Expression of Immune-Regulatory Genes Associated with PD-L1 Display in Melanoma: Implications for PD-1 Pathway Blockade. Clin Cancer Res 2015.
85. Yuan J, Gnjatic S, Li H, et al. CTLA-4 blockade enhances polyfunctional NY-ESO-1 specific T cell responses in metastatic melanoma patients with clinical benefit. Proceedings of the National Academy of Sciences of the United States of America 2008;105:20410-5.
86. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014;515:568-71.
87. Smith LK. HLA typing by direct DNA sequencing. Methods Mol Biol 2012;882:67-

19. ATTACHMENTS

- Consent Form
- Genentech Safety Reporting Fax Cover Sheet
- Guidelines for Affiliate Institutions in Multicenter Studies

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

Submit AEs/SAEs/ AESIs/ Pregnancy reports to
AE / SAE FAX No: (650) 225-4682Alternate Fax No: (650) 225-4630

Genentech Study Number	ML29820
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

20. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

1. Multi-site Communication:

The CPDM office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM office will coordinate regularly scheduled conference calls with affiliate sites.

The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

3.1 Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected prior to the initiation of an affiliate site.

- CV of PI, Sub-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Sub-I's (current copy)
- Human subjects training certificates for PI and Sub-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)

- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

3.2 Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to Q3153@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s)/correspondence should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. As per HICCC directives, no eligibility waivers will be granted by the PRMC/DSMC for HICCC Investigator Initiated Trials.

5. Guidelines for Affiliate Site Monitoring

5.1 On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    - The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

5.2 MCT Remote Monitoring:

1. When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.

2. Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.

3. Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case-by-case basis.

4. The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.

- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.

- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:

    - Informed consent procedures
    - Eligibility criteria
    - Protocol specific treatment compliance
    - Protocol specific toxicity/outcome documentation/compliance
    - Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    - Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    - Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    - Pharmacy accountability records
    - Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)

- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

6. Dose Level Determinations:

The sponsor-investigator will review enrollment for each dose level cohort during the regularly scheduled conference call with the affiliate sites.

The dose level for newly enrolled subjects will be determined by the study statistician upon notification that a subject has signed informed consent to participate in the study. The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study.

If a Dose Limiting Toxicity (DLT) is identified in a subject, the affiliate site must notify the sponsor-investigator via email at the study specific email address within 1 business day of identification. The lead site will communicate that a DLT has been experienced within 1 business day.

7. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g. 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.
If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.