
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GINA M DAVIS
11/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117296

**MEETING REQUEST-
WRITTEN RESPONSES**

Genentech, Inc.
Attention: Fojan Zamanian
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Zamanian:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MPDL3280A.

We also refer to your submission dated April 25, 2013, containing a Type C meeting request. The purpose of the requested meeting was to discuss the proposed nonclinical safety and clinical pharma ogy strategies to support future development and registration of MPDL3280A.

Further reference is made to our Meeting Granted letter dated May 10, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 25 2013, background package.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	IND
Application Number:	117296
Product Name:	MPDL3280A
Indication:	For the treatment of Non-Small Cell Lung Cancer (NSCLC)
Sponsor/Applicant Name:	Genentech, Inc
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

On April 25, 2013, Genentech submitted a Type C meeting request to discuss the proposed nonclinical safety and clinical pharmacology strategies to support future development and registration of MPDL3280A. MPDL3280A is indicated for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1-positive, as determined by an FDA-approved test, after failure of a platinum-containing chemotherapy regimen.

Genentech states that MPDL3280A is a phage-derived human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that targets PD-L1 and inhibits its interaction with PD-1 and B7.1. The antibody consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each) and is produced in Chinese hamster ovary (CHO) cells.

MPDL3280A is administered as a fixed dose (equivalent to an average body-weight-based dose of 15 mg/kg) of 1200 mg by an intravenous (IV) infusion every 3 weeks (Q3W; 21 days) for 16 cycles was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below.

Nonclinical toxicology studies conducted to support the clinical development of MPDL3280A are listed in Table 1.

Table 1 - Summary of Completed MPDL3280A Nonclinical Studies

Study No.	Study Type	Dose Level	Treatment and Recovery Duration	Additional Assessments
08-0806	15-day, pilot, toxicology study in mice (non-GLP)	0 mg/kg 10 mg/kg 50 mg/kg	15 days (Q1W; 3 total doses) with 4-week recovery	Serum cytokines, immunophenotyping (T cell activation markers)
08-1148	8-Week intravenous or SC toxicology study in monkeys (GLP)	0 mg/kg 5 mg/kg 15 mg/kg 50 mg/kg	8 weeks (Q1W; 9 total doses) with 12-week recovery	Safety pharmacology (cardiovascular, respiratory and neurological), immunophenotyping (T cell activation markers), serum cytokines, NK cell activity, auto-antibodies
08-1172	Hemolytic potential and blood compatibility (GLP)	NA	NA	NA
08-1174	Cross-reactivity in human and cynomolgus tissues (GLP)	NA	NA	NA

FDA=Food and Drug Administration; GLP=Good Laboratory Practice; NA=note applicable; NK=natural killer; Q1W=once every week; SC=subcutaneous.

Note: The GLP studies listed above are being conducted in accordance with U.S. FDA GLP regulations (21 CFR, Part 58).

Current clinical studies of MPDL3280A are shown in Table 2. The sponsor's proposed clinical development plan for MPDL3280A in NSCLC is shown in Table 3.

Table 2 - Summary of Ongoing MDPL3280A Clinical Studies

Protocol No.	Patient Population	Target No. of Patients Planned	No. of Patients Enrolled[a]	Study Design
PCD4989g	Solid tumors & hematologic malignancies	314	175	Phase Ia, single-agent; MPDL3280A Q3W; up to 1 year; dose-escalation and expansion cohorts
GP28328	Solid tumors	65	4	Phase Ib, in combination with Bev alone (in solid tumor patients; MPDL3280A Q3W+Bev 15 mg/kg Q3W) or with Bev plus FOLFOX (in OX-naïve CRC patients; MPDL3280A Q2W+Bev 10 mg/kg Q2W+FOLFOX Q2W); up to 1 year
GP28384	$BRAF^{V600}$-mutation positive melanoma	44	3	Phase Ib, MPDL3280A Q3W in combination with vemurafenib at starting dose levels of 720 and of 960 mg PO BID; up to 1 year

Bev=bevacizumab; BID=twice daily; CRC=colorectal cancer; FOLXFOX=5-fluorouracil, leucovorin, and oxaliplatin; Q3W=every 3 weeks; Q2W=every 2 weeks; OX= Oxaliplatin; No.=number; PO=by mouth.

[a] As of 14 September 2012.

Table 3 - Proposed Clinical Development Plan for MPDL3280A in NSCLC

Study (Projected Initiation)	Tumor Status	Design	Material and CDx Assay	Purpose
GO28625 (Q2 2013)	PD-L1 positive	• Single arm study Phase II • Patient population (n=100): – Metastatic or Locally Advanced NSCLC – PS 0-1 – 2L+ approximately ≥50%, 1L ≤50% • Dose: aPD-L1 as a fixed dose of 1200 mg IV Q3W x 16 cycles • 1°endpoint: ORR per modified RECIST	Phase I material and validated IUO labeled prototype IHC assay	Supportive study for accelerated approval of MPDL3280A
GO28754 (Q4 2013)	PD-L1 positive	• Single arm study Phase II • Patient population (n=200): – Metastatic or Locally Advanced NSCLC – PS 0-2 – 2L+ approximately ≥90% 1L ≤10% • Dose: aPD-L1 as a fixed dose of1200 mg IV Q3W x 16 cycles • Co-Primary endpoints: ORR per modified RECIST and ORR per RECIST 1.1	Phase III material and IUO labeled design-locked IHC assay	Pivotal study for accelerated approval of MPDL3280A
GO28753 (Q2 2013)	PD-L1 positive or negative	• Randomized Phase II vs. docetaxel • Patient population (n=180): – Metastatic or Locally Advanced NSCLC – Stratified by diagnostic status and other baseline prognostic factors – PS 0-1 – 2L/3L • Dose: aPD-L1 as a fixed dose of 1200 mg IV Q3W x 16 cycles • 1°endpoint: OS	Phase I material and validated IUO labeled prototype IHC assay	Supportive study for accelerated approval of MPDL3280A
GO28915 (Q4 2013)	PD-L1 positive or negative	• Randomized Phase III vs. docetaxel • Patient population (n=600): – Metastatic or Locally Advanced NSCLC – Stratified by diagnostic status and other baseline prognostic factors – PS 0-1 – 2L/3L • Dose: aPD-L1 as a fixed dose of 1200 mg IV Q3W x 16 cycles • 1°endpoint: OS in patients with PD-L1-positive NSCLC (OS in overall population regardless of PD-L1 status will be tested in hierarchical fashion)	Phase III material and IUO labeled design-locked IHC assay	Proposed study for conversion to full approval of MPDL3280A

Q2=second quarter, Q3= third quarter; Q4=fourth quarter; NSCLC=non-small cell lung cancer; PS=performance status; IV=intravenous; Q3W=every three weeks; ORR=overall response rate; RECIST=Response Evaluation Criteria in Solid Tumors; IUO=investigational use only; IHC=immunohistochemistry; OS=overall survival.

2.0 OBJECTIVES

- To obtain agreement on the proposed nonclinical safety and clinical pharmacology strategies that will be used to enable future clinical development and registration.

3.0 QUESTIONS AND RESPONSES

Nonclinical

1. Does the Agency agree that the completed nonclinical toxicology data combined with the available clinical data from PCD4989g are adequate to support initiation of the proposed GO28625, GO28754, GO28753, and GO28915 studies in NSCLC?

   FDA response: Yes, the nonclinical toxicology data appear adequate to support the proposed clinical trials.

2. Does the Agency agree that the completed nonclinical toxicology data combined with the available clinical data from the PCD4989g, GO28625, GO28754, GO28753, and GO28915 studies are adequate to support a future BLA for NSCLC and other advanced cancer patient populations that fall under ICH S9 Guidance (Nonclinical Evaluation for Anticancer Pharmaceuticals)?

   FDA response: Yes, based on the pharmacokinetics at 20 weeks of MPDL3280A in the 9-injection study conducted in cynomologus monkeys, and considering the increased dose intensity of this study (weekly) compared to the intended clinical schedule (Q3W), the completed general nonclinical toxicology studies described in the meeting package are sufficient to support the submission of a future BLA for NSCLC and other advanced cancers that fall under the ICH S9 Guidance.

3. Does the Agency agree that the completed nonclinical toxicology data combined with the available clinical data from the PCD4989g, GO28625, GO28754, GO28753, and GO28915 studies are adequate to support a (b) (4) ?

   FDA response: No. The nonclinical toxicology data do not appear adequate to support a (b) (4). For further guidance, refer to ICH S6 Guidance for Industry: Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074957.pdf; and ICH S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf.

4. Embryo-fetal loss following programmed cell death1 (PD-1)/PD-L1 inhibition has been

clearly demonstrated in the literature and is described in this package. Per ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals guidance and ICH S6 (R1) Guidance (Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals), does the Agency agree that additional embryo-fetal, fertility, and peri-postnatal development studies would not further inform clinical practice or risk management and are thus not required for registration?

FDA response: FDA requires an assessment of a biological product's developmental and reproductive toxicology in order to support an appropriate labeling statement regarding its safety with respect to relevant patient sub-populations. Such an assessment is generally conducted by measuring "the toxicological effects of the drug in animals and in vitro." 21 CFR 312.23(a)(8)(ii).

In this case, FDA may accept an assessment of MPDL3280A's developmental and reproductive toxicology that does not include studies of MPDL3280A in animals to support a BLA submission for the treatment of patients with advanced cancer. An approach of reliance on generally accepted scientific knowledge may be appropriate in this case given the nature and quality of the evidence Genentech has cited.

Either at the time of or prior to a future BLA submission, submit relevant data and information (including non-product-specific published literature such as the papers referenced in the meeting package) that generally explains the effects with respect to fetal development on blocking the PD-1/PDL1 signaling pathway during pregnancy to support an appropriate labeling statement for the product. Include copies of any specific literature reports used to support the reproductive toxicology assessment in the BLA submission. Any mechanistic studies intended to support Genentech's assessment should be conducted in compliance with the regulations for Good Laboratory Practices (21 CFR part 58). Genentech may not rely on product-specific published literature describing studies of other biological products, including studies regarding a licensed biologic product, for an assessment of the developmental and reproductive toxicology of MPDL3280A.

Clinical Pharmacology

5. Does the Agency agree with the proposed strategy to assess comparability between Phase I and Phase III material for MPDL3280A?

FDA response: Insufficient information has been provided to perform a comparability risk assessment. The extent of clinical data needed to support comparability will depend, in part, upon the details of the proposed manufacturing changes along with the degree to which analytical and non-clinical data support comparability. In the event that the Phase I and Phase III materials for MPDL3280A do not appear comparable based on analytical and non-clinical data, a cross-study comparison with sparse pharmacokinetic (PK) sampling as proposed will not be adequate to assess the PK comparability of these two materials.

6. Does the Agency agree that dedicated drug-drug interaction (DDI) studies for MPDL3280A are not required?

   FDA response: The proposed plan to conduct population analyses and assess the effects of MPDL3280A on cytokines in Study PCD4989g appears reasonable to assess the potential for drug interactions with MPDL3280A. The results of these analyses and assessments will determine the need for any dedicated drug interactions studies.

7. Does the Agency agree with the proposed pharmacokinetic (PK) assessment strategy in special populations for MPDL3280A?

   FDA response: Yes. The proposed sparse PK sampling across multiple clinical trials to perform population PK analyses with a covariate evaluation, including but not limited to age, weight, estimated creatinine clearance, and liver function appears reasonable. The adequacy of the data and analyses will be reviewed upon submission of the BLA.

8. Does the Agency agree with the proposed strategy for assessment of immunogenicity in the GO28625, GO28754, GO28753, and GO28915 studies, which does not include an assessment of neutralizing anti-therapeutic antibody (ATA) activity?

   FDA response: No, FDA does not agree. The tiered approach should include an assay to measure neutralizing antibodies. While immunogenicity risk assessments can help determine the ATA testing strategy and the degree to which the ATA responses need to be characterized, insufficient information has been provided to justify the proposed strategy. For example, the data in Table 12 of the meeting package suggest a relatively high immunogenicity rate for MPDL3280A.

   FDA recommends that a sensitive neutralizing antibody assay with acceptable drug tolerance be developed and included in the immunogenicity assessments for studies GO28625, GO28754, GO28753, and GO28915. Of note, as MPDL3280A appears to act only through blocking PD-L1, the use of a non-cell based binding assay to detect neutralizing antibodies may be acceptable if sufficiently justified.

   In addition, the immunogenicity sampling plan should capture the baseline, the early onset of the ATA and its dynamic profile (transient or persistent).

9. Does the Agency agree that the high quality ECG interval data provided in this package from the Phase Ia study (PCD4989g) adequately assesses the risk for MPDL3280A effect on QTc prolongation?

   FDA response: The ECG interval data provided in this package appear to be adequate; however, the final determination of the acceptance of the data to adequately assess the risk for MPDL3280A to prolong the QT/QTc interval will be made at the time of the

BLA review. FDA recommends that ECG monitoring in future clinical studies include baseline and periodic on therapy ECGs.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GINA M DAVIS
07/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Pre-IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Fojan Zamanian
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Zamanian:

Please refer to your Pre-Investigational New Drug Application (PIND) file for MPDL3280A.

We also refer to the teleconference between representatives of your firm and the FDA on February 12, 2013. The purpose of the meeting was to discuss the clinical development program of MPDL3280A in the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Appendix 1 - RECIST version 1.1

Reference ID: 4006797

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-IND/Clinical Development Program
Meeting Date and Time:	February 12, 2013
Application Number:	117296
Product Name:	MPDL3280A
Indication:	Locally advanced or metastatic NSCLC
Sponsor/Applicant Name:	Genentech, Inc.
Meeting Chair:	Patricia Keegan
Meeting Recorder:	Gina Davis

FDA ATTENDEES

Anthony Murgo, M.D Associate Director, Office of Hematology and Oncology
Patricia Keegan, M.D., Director, Division of Oncology Products 2
Lee Pai-Scherf, M.D., Medical Officer, Division of Oncology Products 2
Gideon Blumenthal, M.D., Acting Medical Team Lead, Division of Oncology Products 2
Gina Davis, M.T., Regulatory Health Project Manager, Division of Oncology Products 2
Stacy Shord, Pharm.D., Clinical Pharmacology and Genomics Reviewer, Office of Clinical Pharmacology V
Rosane Charlab Orbach, Ph.D., Acting Genomics Team Lead, Office of Clinical Pharmacology
Yuan Li Shen, Dr. PH., Statistics Reviewer, Office of Biostatistics
Elizabeth Mansfield, Ph.D. Director, Personalized Medicine, Office of In-Vitro Diagnostics, CDRH
Caryl Giuliano, Ph.D., Office of In Vitro Diagnostics, CDRH
Prakash Jha, M.D., Medical Officer, Office of In Vitro Diagnostics and Radiological Health, CDRH
Donna Roscoe, Ph.D., Acting Branch Chief, Office of In Vitro Diagnostics and Radiological Health, CDRH

SPONSOR ATTENDEES

Genentech, Inc.
Chris Bowden, M.D. Vice President, Product Development Clinical Oncology
Zach Boyd, M.Sc. Manager, Companion Diagnostics
Nicholas Bruno Associate Group Director, Product Development Regulatory
Bruce McCall, M.D., Safety Science Leader, Safety Science
Daniel Chen, M.D., Ph.D. Associate Group Director, Product Development Clinical Oncology
Gregg Fine, M.D. Associate Medical Director, Product Development Clinical Oncology
Marcin Kowanetz, Ph.D. Scientist, Oncology Biomarker Development
Maya Leabman, Ph.D. Scientist, Preclinical and Translational Pharmacokinetics
Ben Lyons, Ph.D. Associate Director, Biostatistics

Reference ID: 4006797

Ahmad Mokatrin, Ph. D. Principal Statistical Scientist, Biostatistics
Mark Stroh, Ph.D. Senior Scientist, Clinical Pharmacology
Mark Velligan, Project Team Leader, Portfolio Management and Operations
Fojan Zamanian, Associate Program Director, Product Development Regulatory

Ventana
Brian Baker, Regulatory Affairs, Ventana Medical System

1.0 BACKGROUND

On December 21, 2012, Genentech, Inc. (Genentech) submitted a Type B, phase 1a meeting request to the Division of Oncology Products 2 (DOP 2) to discuss the clinical data from the ongoing phase 1a study PCD4989g and the proposed development plan to support accelerated approval of MPDL3280A for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with PD-L1 positive tumor status, after failure of platinum-containing chemotherapy regimen.

MPDL3280A is a phage-derived human IgG1 monoclonal antibody (mAb) that binds PD-L1 and inhibits its interaction with PD-1 and B7.1. The initial IND for MPDL3280A was submitted in April 2011 (IND111271). Genentech is currently conducting three phase I studies under IND 111271: PCD4989g, a phase 1a, dose escalation and expansion cohort study in patients with advanced malignancies; GP28328, a phase 1 study of MPDL3280A in combination with bevacizumab or with bevacizumab plus FOLFOX in patients with advanced solid tumors and GP28384, phase 1a study of MPDL3280A in combination with vemurafenib in patients with previously untreated BRAFV600-mutation positive metastatic melanoma.

As of September 2012, a total of 175 have been enrolled in study PCD4989g and exposed to MPDL3280A monotherapy at doses between 0.01 and 20 mg/kg. The maximum-tolerated dose (MTD) was not reached and no dose-limiting toxicities (DLT) have been reported at any dose level studied. The study enrolled 53 patients with advanced NSCLC (10 squamous, 43 non-squamous histology), 55 with renal cell cancer (RCC), 44 with advanced melanoma, 6 with head and neck carcinoma, 5 with colon cancer and 12 with other malignancies. Serious adverse events (SAE) were reported in 21.7% of the patients and include fatigue, malaise, cough, liver enzyme elevation, CPK elevation, hypoxia, bone pain, systemic inflammatory response syndrome, ataxia and abdominal pain. Immune-related AEs include rash (12%, one grade 3), hypothyroidism (two grade 2), elevated transaminases/hepatitis (four grade ≥ 3), myasthenia graves/myositis (one grade 2) and colitis (one grade 2). Objective responses have been observed in patients with NSCLC, RCC, melanoma, gastric, colorectal, and head and neck cancer. In NSCLC, partial remission was reported in 8/38 evaluable patients (21%): 4/4 had PD-L1 positive tumor, 1/23 PD-L1 negative tumor, 3/11 with PD-L1 status unknown. Tumor response was observed at doses of 1, 10, 15 and 20 mg/kg. The duration of response was not reported. PD-L1 tumor expression using formalin-fixed, paraffin-embedded tissue was retrospectively determined by immunohistochemistry using an anti-PD-L1 specific antibody (SP142) developed by Genentech.

Based on the preliminary efficacy data from PCD4989g, Genentech plans to submit a future BLA for the use of MPDL3280A as monotherapy in patients with advanced NSCLC that is PD-L1-positive, after failure of a platinum-containing chemotherapy regimen. The proposed clinical development plan for MPDL3280A in NSCLC include the following three studies summarized below:

GO28625 - is a single-arm, phase 2 study, in 100 patients with stage IIIB or IV NSCLC who will be administered phase 1 clinical trial material. Patients will be selected for PD-L1-positive tumor status using a PD-L1 IHC assay. Three cohorts are planned: cohort 1, patients who have not received prior chemotherapy for advanced disease (45%), cohort 2, patients who have progressed during or following a prior platinum-based chemotherapy (45%) and cohort 3, will enroll either first-line or previously-treated patients with (ECOG 2) decreased performance status (10%). MPD3280A at a dose of 15 mg/kg will be administered intravenously on day 1 of a 21-day cycle for a maximum of 16 cycles (or 12 months, whichever occurs first) until unacceptable toxicity or symptomatic deterioration attributed to disease progression. Clinically stable patients can continue treatment after progression per modified RECIST criteria if the risk/benefit ratio is judged to be favorable by the investigator. The primary endpoint is investigator-assessed objective response rate (ORR) according to modified RECIST. Secondary endpoints are investigator-assessed ORR per RECIST1.1, duration of response (DOR), progression-free survival (PFS) and overall survival (OS). The sample size of 100 is proposed to reject a null hypothesis of an ORR rate of 26% or lower versus an alternative of 40% with 82% power assuming a 2-sided alpha level of 5%. This sample size also assures that the ORR will be estimated using a 95% confidence interval (CI) with a maximum width of 19.6% (± 9.8%). The analysis of primary and secondary efficacy parameters will include all patients who receive at least one dose of study drug (combined cohorts 1, 2 and 3) and will be conducted with patient data collected through approximately 6 months after the last patient is enrolled in the study. No adjustments for multiplicity of endpoints will be incorporated in the efficacy analyses. For the primary efficacy analysis, an ORR point estimate and 95% CI will be computed using the Blyth-Still-Casella method.

GO28754 - is intended to support accelerated approval of MPDL3280A. The study is a single-arm, phase 2 study, in patients with PD-L1-positive NSCLC who will be administered Phase 3 clinical trial material. The study will enroll approximately 200 patients: up to 10% will be patients who have not received prior chemotherapy for advanced disease (cohort 1); ≥ 80 % will be patients who have progressed during or following a prior platinum-based chemotherapy (cohort 2); and 10% will be either first-line or previously-treated patients with decreased performance status (ECOG 2) (cohort 3). The primary endpoint is investigator-assessed immune-related ORR according to modified RECIST. Secondary endpoints include investigator assessed ORR, DOR and PFS according to RECIST 1.1; and OS and independently-reviewed ORR per modified RECIST. The sample size of 200 is proposed to reject a null hypothesis of an ORR rate of 30% or lower versus an alternative of 40% with 82% power assuming a 2-sided alpha level of 5%. This sample size also assures that the ORR will be estimated using a 95% CI with a maximum width of 13.8% (± 6.9%). The analysis of primary and secondary efficacy parameters will include all patients who receive at least one dose of study drug

and will be conducted with patient data collected through approximately 6 months after the last patient is enrolled in the study. No adjustments for multiplicity of endpoints will be incorporated in the efficacy analyses. For the primary efficacy analysis, an ORR point estimate and 95% CI will be computed using the Blyth-Still-Casella method.

GO28753 - is a Phase 2/3, open-label, randomized, controlled study designed to evaluate the efficacy and safety of MPDL3280A in patients with locally advanced or metastatic NSCLC who experienced disease progression during or following platinum-based therapy. The study includes two parts:

- Part 1 (GO28753-1) is a randomized, phase 2, trial in patients selected for PD-L1-positive tumors who will be administered phase 1 clinical material. Approximately 100 patients will be stratified by the number of prior chemotherapy regimens (1 vs. 2) and histology (nonsquamous vs. squamous) then randomized 1:1 to receive either MPDL3280A at a dose of 15 mg/kg on day 1 of each 21-day cycle for a maximum of 16 cycles or docetaxel at a dose of 75 mg/m^2 on day 1 of each 21-day cycle until disease progression. The primary endpoint is OS. The Secondary endpoints are DOR, PFS and 1-year and 2-year OS rate between the two treatment groups with 58 events observed and an observed hazard ratio (HR) of 0.5, the 90% CI for the true HR is expected to be 0.34-0.82. Additionally, the estimated power will be 75% to detect an OS HR of 0.5 (corresponding to an improvement in median OS from 8 to 16 months) assuming proportional hazards and a 2-sided significance level of 0.05. The focus of the analysis in Part 1 is estimation of the HR.

- Part 2 (GO28753-2) is a randomized, phase 3 trial in which patients will be administered phase 3 clinical material. The study will include both PD-L1 positive and PD-L1 negative patients. Approximately 600 eligible patients will be stratified by PD-L1 status by IHC (up to four categories of PD-L1 expression), the number of prior chemotherapy regimens (1 vs. 2), histology (nonsquamous vs. squamous) and randomized 1:1 to receive either MPDL3280A or docetaxel. The primary endpoint is OS and two hypotheses will be tested: first testing the primary hypothesis in patients with PD-L1-positive NSCLC and then testing in the secondary hypothesis based on the overall population.

  Part 2 will enroll approximately 180 PD-L1-positive patients and approximately 600 total patients. A minimum of 20% of patients enrolled in Part 2 (in both in the PD-L1 positive and overall populations) will have squamous histology. Part 2 of the study requires approximately, 89 and 323 deaths in the PD-L1 positive population and overall population, respectively. Assuming 1-sided significance level of 0.025 and with 90% power, the estimated numbers of event are obtained to detect a difference in median OS of 8 vs.16 months (corresponding to a HR of 0.50) in the PD-L1 positive subgroup. In addition, the estimated numbers of event are obtained to detect a difference in median OS of 8 vs. 11.5 months (corresponding to a HR of 0.69) in the overall population. The sample size calculation also assumes proportional hazards, a dropout rate of 5% per 18

months and 30% of the patients are PD-L1 positive. Genentech indicates that each part of the study will be analyzed separately and efficacy data from Part 1 will not be combined with data from Part 2. Results from Part 1 of study GO28753 will be used to amend Part 2 of the study prior to the evaluation of efficacy of the Part 2 (e.g., amend the sample size or revise the definition of cutoff for PD-L1 positivity status). In Part 2, the hierarchical alpha spending method will be applied to test the primary hypothesis in the PD-L1 positive patients and then the secondary hypothesis in the overall population with respect to the primary endpoint (OS) if the first test achieves statistical significance. The primary analysis for OS will be a stratified log-rank test.

2.0 OBJECTIVE

- To discuss the clinical data from the ongoing Phase 1a study (PDC4989g) and Genentech's/Roche's proposed development plan to support accelerated approval of MPDL3280A.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Clinical

The proposed studies GO28625, GO28754, and GO28753 (Part 1 and 2) are designed to characterize the efficacy and safety of MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1-positive.

1. Does the Agency agree with the target population of patients with PD-L1-positive NSCLC in all three studies as described in Section 8.4?

   FDA response: FDA agrees that the target population of patients with PD-L1-positive NSCLC in the planned studies is supported by the product's pharmacodynamic effects, however, FDA does not agree with the inclusion of patients with locally advanced or metastatic NSCLC who have not received a platinum-containing regimen in studies GO28625 and GO28754. While preliminary data suggests that MPDL3280A has anti-tumor activity in PD-L1 positive tumors, data available to date is limited. Multiple randomized controlled studies have shown the cisplatin-based chemotherapy improves survival and palliates disease-related symptoms and is the current standard of care for this population.

   The patient informed consent should include a discussion of the FDA approved therapeutic options for second line therapy.

   Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 1: Patients with locally advanced or metastatic PD-L1-positive NSCLC who have not received a platinum-containing regimen are included in studies GO28625 and GO28754 in order to increase the experience in this patient population. (b) (4)

[redacted] (b) (4) . Given the standard of care available to 1L NSCLC patients, it will be critical to provide appropriate and complete informed consent. As per the suggestion in FDA's letter of 19 Dec 2012 regarding PCD4989g, we propose to include language in the ICF for GO28625 and GO28754 to clearly inform patients of standard therapies in 1L NSCLC.

Discussion during the teleconference: FDA requested updated information regarding NSCLC cohort. Genentech stated that there is no updated information, noting that there are data only for 38 patients with adequate follow-up with a response rate of 24% across all patients (unselected population) and 4 objective responses in the four patients with PD-L1 positivity by the current clinical trials assay method. FDA acknowledged Genentech's response, but advised Genentech that information obtained more than 9 months ago (data cut-off date of July 1, 2012) was not adequate. FDA advised Genentech to provide updated information on response rates and updated information on response duration; FDA also agreed to evaluate the Informed Consent Document for its adequacy.

Regarding the single arm trial, GO28754, which is intended to support a request for accelerated approval.

2. Does the Agency agree that the proposed treatment population in study GO28754 (i.e., patients with locally advanced or metastatic NSCLC who progress during or after standard platinum-based chemotherapy) represents a patient population with an unmet medical need appropriate for consideration for accelerated approval under 21 CFR part 601, subpart E?

FDA response: No. Current therapy available for patients with locally advanced or metastatic NSCLC who progress during or after standard platinum-based chemotherapy include the FDA-approved agents: docetaxel, erlotinib and pemetrexed. In order to be considered for accelerated approval under 21 CFR part 601, subpart E, MPDL3280A must demonstrate meaningful therapeutic benefit in this population over existing treatments (e.g., ability to treat patients unresponsive to or intolerant of, available therapy, or improved patient response over available therapy).

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 2: Study GO28754 will be modified to ensure enrollment of approximately 100 patients that have received at least one additional therapy following platinum-based chemotherapy.

Outcomes for NSCLC patients that have progressed following standard platinum-based chemotherapy remain exceedingly poor, with ORR in the range of 5-10% and OS ranging between 6-10 months. Many of these patients will no longer be eligible to receive further therapies following SOC chemotherapy in the 2L due to declining performance status. Based upon this we propose to allow treatment of these patients in study GO28754, and will report efficacy and safety outcomes in the entire study population, as well as in each

subset of patients based on prior therapy. We would like to explore with you whether additional information or changes should be included.

Discussion during the teleconference: FDA agreed that patients whose disease has progressed following second line therapy is a population with unmet medical need, however, a controlled study would be necessary to show that MDPL3280A is superior to available treatment in patients with progression after only first-line therapy. In response to Genentech's question, patient's who receive first-line therapy followed by pemetrexed maintenance would not be considered to have an unmet medical need, i.e., no available therapy. Genentech acknowledged FDA's response.

3. Does the Agency agree that the GO28754 study with a primary endpoint of objective response rate (ORR) according to modified RECIST as described in Appendix A-1, could be acceptable for filing and review to support accelerated approval of MPDL3280A as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1-positive, after failure of a platinum containing chemotherapy regimen?

FDA response: No. Please see FDA's response to question 2. In addition, please note that the use of modified RECIST to determine tumor response is considered exploratory however, demonstration of a clinically meaningful response rate with adequate duration determined by independent review based on RECIST version 1.1 as the primary analysis could be supported by response rates using modified RECIST.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 3: Sponsor proposes to make RECIST 1.1 by independent review and response by modified RECIST as co-primary endpoints.

Discussion during the teleconference: FDA stated that this proposal is acceptable; however for US regulatory purposes, FDA considers only tumor-based endpoints according to RECIST 1.1 as the results intended to support a regulatory action. Tumor-based endpoints determined with the proposed modifications to RECIST 1.0 or 1.1, as described in Appendix 1 to these minutes, will be considered exploratory. Please refer to the Guidance for Industry: "*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

4. Does the Agency agree that the proposed treatment population in study GO28753 (i.e., patients with locally advanced or metastatic NSCLC who progress during or after standard platinum-based chemotherapy) is adequately defined per the eligibility criteria in the study protocol synopses?

FDA response: Yes. The proposed population for study GO28753 is adequately defined.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 4: Genentech acknowledges the Agency's feedback and does not require further discussion on question.

Discussion during the teleconference: FDA acknowledged Genentech's response and no discussion occurred.

5. Does the Agency agree that the GO28753-2 study as designed with docetaxel as the comparator can establish clinical benefit of MPDL3280A treatment based on a primary analysis of OS in patients with locally advanced or metastatic NSCLC that is PD-L1-positive, after failure of a platinum-containing chemotherapy regimen?

FDA response: Yes, provided that the sub-group is based on the randomized population and not on the retrospectively determined PD-L1 positivity cut-off.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 5: The definition of PD-L1-positivity will be defined prior to the initiation of GO28753-2. There is the potential that this definition will be modified in the statistical analysis plan and protocol of GO28753-2 to another set of predefined diagnostic strata prior to the unblinding of this study. These changes will be based on data that is entirely external to GO28753-2. There is no plan to use the data from GO28753-1 to modify the definition of the stratification factors in GO28753-2. The definition of PD-L1 stratification factors of GO28753-2 will not be changed after the first patient is randomized into GO28753-2. However, the definition of PD-L1 positivity (rather than the definition of the stratification factors themselves) may be modified in such a way that different sets of stratification levels are used for the definition of positivity.

Discussion during the teleconference: FDA stated that Genentech will need to provide more detailed information concerning the definition of PD-L1-positivity and how it will be used in the planned analysis for FDA review. Genentech acknowledged FDA's response and will provide the detailed information prior to the Phase 3 study.

6. With respect to the statistical analysis plan for the GO28753 study, does the Agency agree that the results of GO28753-1 could be used to amend Study GO28753-2 (stratified by PD-L1 status) prior to the evaluation of efficacy of GO28753-2 (e.g., sample size or definition of cutoff for PD-L1 positivity)?

FDA response: FDA does not object to use of the results of GO28753-1 to amend Study GO28753-2, with regard to sample size adjustment prior to the evaluation of efficacy of GO28753-2, provided that a detailed statistical analysis plan with regard to the sample size re-estimation based on the Part 1 data is pre-specified.

The proposal to amend the ongoing Part 2 of the protocol to modify the stratification variable for PD-L1 positivity is problematic because the patients stratified within the PD-L1 positive subgroup using the prior positivity cut-off definition can not represent treatment effects in the patients enrolled after amendment using a different cut-off. In

addition, if the results differ in the pre- and post-modification populations, the clinical study results will be extremely difficult to interpret.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 6: In the analysis plan of GO28753-1 we propose to provide guidelines and examples of possible sample size adjustments that can be made to GO28753-2 in lieu of pre-specification. The data from GO28753-1 will not be combined with data from GO28753-2. The data from GO28753-1 is entirely external to GO28753-2.

There is no plan to use the data from GO28753-1 to modify the definition of the stratification factors in GO28753-2. The definition of PD-L1 stratification factors of GO28753-2 will not be changed after the first patient is randomized into GO28753-2. However, the definition of PD-L1 positivity (rather than the definition of the stratification factors themselves) may be modified in such a way that different sets of stratification levels are used for the definition of positivity.

Discussion during the teleconference: Genentech stated that more examples will be provided regarding the proposed strata. FDA stated that changes to the PD-L1 cut-off during the conduct of the trial is problematic, since randomization will not have been stratified by the "new" PD-L1 definition. Genentech will provide a plan regarding more information of the proposal for data analysis based on the PD-L1-status.

7. Does the Agency agree that the proposed hierarchical alpha spending proposal, Study GO28753-2 could also establish benefit in the overall population (i.e., independent of PD-L1 status) based on an OS endpoint?

FDA response: FDA does not object to the proposed hierarchical testing procedure, however, if a positive result for the overall population is mainly driven by the PD-L1 positive subgroup, only the result from the PD-L1 positive subgroup will be considered for labeling purpose.

Also, FDA would request a more detailed analysis plan to be submitted with regard to the timing of the analysis (based on the number of events) for the PD-L1 positive subgroup and overall population.

FDA notes that Genentech also proposed a sequential gating approach to be employed to test the two hypotheses in order to control the overall level of significance level (Dmitrienko 2010) in the company's position section. However, Genentech did not provide any description of this proposal. Please provide more detailed information.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question #7: Currently, the final OS analysis for GO28753-2 is planned to be performed when approximately 89 and 323 events both occur in the PD-L1 positive and the ITT populations respectively. We will further describe this in the analysis plan for GO28753-2.

The primary and secondary hypotheses related to overall survival (OS) will be tested in Part 2 of study GO28753. The first null hypothesis (corresponding to the primary objective) will be that there is no difference in OS between the two treatment arms in the subset of PD-L1 positive patients. The second null hypothesis (corresponding to the secondary objective) will be that there is no difference in OS between the two treatments in the overall population (ITT population). In order to control the overall alpha level, the two null hypotheses will be tested using a hierarchical fixed-sequence procedure as described in section 2.6.3 of Dmitrienko (2010). We will further describe this in the analysis plan for GO28753-2.

Discussion during the teleconference: FDA acknowledged Genentech's February 12, 2013, electronic (email) containing additional information as requested in FDA's response to question # 7. No discussion occurred.

Clinical Pharmacology

8. Does the agency agree with the described strategy for dose selection?

FDA Response: The strategy for dose selection appears reasonable. In addition, FDA recommends evaluation of the relationship between pharmacokinetics of MPDL3280A and body size to determine which dosing approach (i.e., body size-based vs. fixed dosing) results in less inter-subject variability and use that dosing approach for future clinical efficacy and safety trials.

There is insufficient information to determine the safety of the proposed duration of dosing (sixteen 21-day cycles). Additional data should be provided as it becomes available.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 8: We have performed an evaluation to contrast estimated exposure of MPDL3280A following fixed- and weight-based dosing. Simulations do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight (methods as described in Bai et al. 2012). Based on this analysis we plan to use a fixed dose in studies GO28625, GO28754 and GO28753. We will provide this evaluation in the IND 117296 with protocol GO28625.

Bai S, Jorga K, Xin Y,et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet. 2012;51(2):119-35.

Discussion during the teleconference: FDA acknowledged Genentech's February 12, 2013, electronic (email) containing additional information regarding the approach to dosing in response to FDA's response to question # 8, and no discussion occurred.

Companion Diagnostics

9. Does the Agency agree that a coordinated review with CDRH is warranted to support accelerated approval of both MPDL3280A and the PD-L1 companion diagnostic in the proposed indication based on pivotal study data?

FDA response: Yes. Please note that patient selection and enrollment into the trials that support accelerated approval of both MPDL3280A and the PD-L1 companion diagnostic, should not begin until Genentech has provided demonstration of analytical robustness at the clinical decision point (cut-off) with a pre-specified testing protocol to the agency. FDA recommends that Ventana Medical Systems submit a pre-Submission to CDRH to discuss the analytical validation data. Please see the pre-Submission guidance, "*Medical Devices: Pre-Submission Program and Meetings with FDA Staff*" for further information on the pre-Submission program.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, preliminary response to question # 9: Ventana Medical Systems plans to submit a pre-Submission Meeting to CDRH prior to initiation of single arm trial, GO28754, which is intended to support a request for accelerated approval which will outline the proposed designs of our Analytical Studies for FDA's review (Q2 2013). The detailed results of the analytical studies will be submitted in an IDE no less than 30 days prior to patient screening for the GO28754 trial.

Discussion during the teleconference: FDA acknowledged Genentech's February 12, 2013, electronic (email) containing additional information regarding their plans for a pre-Submission to CDRH in response to FDA's response to question # 9, and no discussion occurred.

ADDITIONAL COMMNETS:

Statistics

10. For the primary analysis population, please clarify that the intent-to-treat population will be used, i.e., patient will be classified based on the randomization code assigned rather than the treatment assigned.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 10: Sponsor intends to classify patients by randomization code assigned.

Discussion during the teleconference: FDA acknowledged Genentech's February 12, 2013, electronic (email) responding to FDA's comment # 10. No discussion occurred.

Clinical Pharmacology

For Study GO28753

11. Recommend excluding patients taking cytochrome P450 3A4 inducers, inhibitors or substrates as the approved labeling U.S. approved docetaxel products states that CYP3A4 substrates, inducers and inhibitor might alter docetaxel metabolism.

    Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 11: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 11.

As part of the development of MDPL3280A, address the following and include the study reports with relevant data in future BLA submission.

12. Characterize the pharmacokinetics and dose proportionality of the MPDL3280A following a single dose and repeated doses.

    Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 12: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 12.

13. Conduct population pharmacokinetic analyses to evaluate the effect of intrinsic and extrinsic factors, including renal and hepatic function on the pharmacokinetics of MDPL3280A, as eligibility criteria appears to permit enrollment of patients with mild to moderate organ impairment. Refer to the FDA Guidance for Industry entitled, "*Population Pharmacokinetics*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf.

    Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 13: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 13.

14. Explore exposure-response relationships of MPDL3280A. Response endpoints should include the clinical efficacy response and toxicity outcome measures, as well as potential biomarkers. Refer to the FDA Guidance for Industry entitled, " *Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf

    Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 14: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 14.

15. Develop and validate the analytical methods used to determine the concentrations of MPDL3280A. Refer to the FDA Guidance for Industry entitled, "*Bioanalytical Method Validation*" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 15: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 15.

16. Conduct immunogenicity testing that takes into consideration the following recommendations:

    a. Develop and validate assays that will be used to detect of binding and neutralizing anti-product antibodies (APA). The validated assays should be capable of sensitively detecting APA responses in the presence of MPDL3280A levels that are expected to be present at the time of patient sampling. Refer to the FDA Guidance for Industry entitled, "*Assay Development for Immunogenicity Testing of Therapeutic Proteins*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf.

    b. Develop immunogenicity sampling plan that captures the baseline, the early onset of the APA and its dynamic profile (transient or persistent).

    c. Evaluate the impact of immunogenicity on pharmacokinetics, pharmacodynamics, tolerability and efficacy of MPDL3280A.

    Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 16: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 16.

17. Evaluate the potential effect of MPDL3280A on the QT/QTc interval. ECGs should be collected at baseline, at maximum and steady-state concentrations, as clinically indicated, and at end of study in clinical trials. Refer to the FDA Guidance for Industry entitled, "*E14 Clinical Evaluation of QT/QTc Interval Prolongation*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

Genentech's February 12, 2013, electronic (email) communication to FDA's February 8, 2013, additional comment # 17: Genentech acknowledges the Agency's feedback and does not require further discussion of additional comment # 17.

Action Items:

- With regard to G028625, Genentech will provide the following information in an amendment to IND 111271 within one month of the February 12, 2012, meeting:

  - A revised protocol, in accordance with agreements reached during the meeting
  - Rationale for the dosing schedule
  - Information on the device
  - modified Informed Consent Document.

- Genentech will provide statistical analysis for the Phase 3 portion protocol GO28753.

- Genentech will request a Type C meeting to reach agreement on the adequacy of their non-clinical safety strategy and clinical pharmacology plan to enable future clinical development and support a marketing application (BLA) for MPDL3280A.

APPENDIX A-1: Modified RECIST

Adapted from Eisenhauer *et al.*, European Journal of Cancer 2009; 45: 228-247, Topalian *et al.*, NEJM 2012; 366:2443-54, and Wolchok *et al.*, Clin Can Res 2009; 15:7412-20.

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents such as MPDL3280A, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

SUMMARY OF MODIFICATIONS FROM RECIST V1.1

	RECIST v1.1	modified RECIST
New lesions	Constitute PD	Do not automatically constitute PD; measurable lesions are added to the sum of the diameters
Definition of PD (measurable lesions)	≥20% increase in sum of diameters relative to the nadir and/or appearance of new lesion(s)	≥20% increase in sum of diameters including new lesions relative to the nadir, confirmed by a consecutive assessment ≥4 weeks later that shows additional measurable increase in measurable lesions
Confirmation of PD	Not required	Allowed if clinically appropriate

In addition, in this protocol, patients will be permitted to continue study treatment even after modified RECIST criteria for progressive disease are met if the risk/benefit ratio is judged to be favorable by the investigator

Definitions of Measurable/Non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will assess response to treatment using modified RECIST.

a. Measurable Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

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

b. Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

Bone scan, PET scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions:

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.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumor Response Evaluation:

Definitions of Target/Non-Target Lesions

a. Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

b. Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases, "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Calculation of Sum of the Diameters:

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

a. Sum of the Diameters at Baseline

The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

b. Sum of the Diameters at Tumor Assessment

For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and *all new measurable lesions* that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment using modified RECIST accounts for the size and growth kinetics of both the old and new lesions as they appear.

Response Criteria:

a. Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

  Note: the appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥ 20% when compared to the sum of the diameters at nadir.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of all target and all new measurable 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.

b. Evaluation of Non-Target Lesions

- **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker level (if applicable). All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)**: Unequivocal progression of existing non-target lesions.

  To achieve unequivocal progression on the basis of the non-target lesions, including non-measurable disease, there must be an overall level of substantial worsening in disease in a magnitude that, even in the presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions, including bone lesions or malignant ascites or pleural or pericardial effusions, is usually not sufficient to qualify for unequivocal progression status. Similarly, the appearance of one or more new non-target lesions, including non-measurable disease, *does not automatically qualify as progressive disease*. The designation of overall

progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will, therefore, be extremely rare.

c. Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Evaluation of Best Overall Response Using Modified RECIST:

a. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

b. Missing Assessments and "Not Evaluable" Designation

When no imaging/measurement is conducted at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table 1. Modified RECIST Time Point Response Definitions

% Change in Sum of the Diameters [a]	Target Lesion Definition	Non-target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Time Point Response
-100%[b]	Complete Response	Complete Response	No	No	CR
-100%[b]	Complete Response	Non-CR/non-PD or not all evaluated	No	No	PR
≤ -30%	Partial Response	Non-PD or not all evaluated	Yes or No	Yes or No	PR
> -30% to < +20%	Stable Disease	Non-PD or not all evaluated	Yes or No	Yes or No	SD
Not all evaluated	Not evaluated	Non-PD or not all evaluated	Yes or No	Yes or No	NE
≥ +20%	Progressive Disease	Any	Yes or No	Yes or No	PD
Any	Any	PD	Yes or No	Yes or No	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[a] Includes measurable new lesions when present.

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

c. Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient is known. According to modified RECIST, a best overall response designation CR or modified PR requires confirmation on a subsequent tumor assessment at least 4 weeks from the date that the response was first documented.

The best overall response according to modified RECIST is interpreted as below:

- **Complete Response (CR):** Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥4 weeks from the date first documented. All lymph nodes short axes must be <10 mm.
- **Partial Response (PR):** Decrease in the sum of the diameters of all target and all new measurable lesions ≥30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥4 weeks from the date first documented.
- **Stable Disease (SD):** Criteria for CR, PR, and PD are not met.
- **Progressive Disease (PD):** Increase in the sum of the diameters of all target and all new measurable lesions ≥20% relative to the nadir, or unequivocal increase in the number or size of non-measurable lesions which may be confirmed by a consecutive assessment ≥4 weeks from the date first documented as follows:
  - The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions, or additional unequivocal increases in the number or size of non-measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST, and patients may achieve a PR or CR based on tumor regression achieved at any time prior to study treatment discontinuation.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GINA M DAVIS
02/27/2013