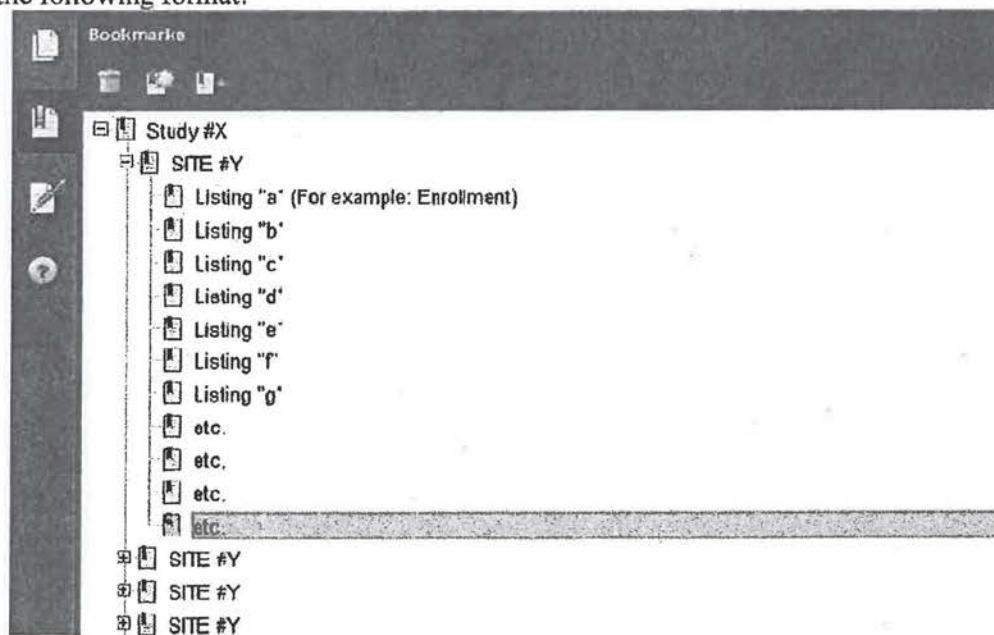


- c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection

Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clnsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```
└─ [m5]
   └─ datasets
      └─ bimo
         └─ site-level
```

- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

“BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions; ESUB@fda.hhs.gov

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
05/14/2015



IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Ms. 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 the meeting between representatives of your firm and the FDA on December 9, 2014. The purpose of the meeting was to discuss the proposed changes to the statistical analysis plans for the ongoing Studies GO28915 (OAK) and GO28754 (BIRCH).

A copy of the official minutes of the meeting 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 (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: IND - Guidance
Meeting Date and Time: December 9, 2014
Meeting Location: CDER WO 22, Room 1315
Application Number: 117296
Product Name: MPDL3280A
Indication: For the treatment of Non-Small Cell Lung Cancer (NSCLC)
Sponsor/Applicant Name: Genentech, Inc.

TENTATIVE FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director, Division of Oncology Products 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Sean Khozin, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Senior Regulatory Health Project Manager, DOP 2

Division of Biostatistics V (DB V)

Shenghui Tang, Ph.D., Statistical Team Lead, DB V
Lijun Zhang, Ph.D., Statistical Reviewer, DB V

Office of In Vitro Radiology

Shyam Kalavar, MPH, CT (ASCP), Reviewer, CDRH/OIR/DMGP

Center for Devices and Radiological Health (CDRH)

Reena Philip, Ph.D., Director, Division of Molecular Genetics and Pathology

SPONSOR ATTENDEES

Cathi Ahearn Lifecycle Team Leader, Global Product Strategy Oncology
Zach Boyd, M.Sc. Senior Manager, Companion Diagnostics
Nicholas Bruno Associate Group Director, Product Development Regulatory
Daniel Chen, M.D., Ph.D. Group Medical Director, Product Development Clinical Oncology
Michael Howland, Ph.D. Program Manager, Product Development Regulatory
Marcin Kowanetz, Ph.D. Scientist, Oncology Biomarker Development
Benjamin Lyons, Ph.D. Associate Director, Biostatistics
Simonetta Mocci, M.D., Ph.D. Medical Director, Product Development Clinical Oncology
Ahmad Mokatrini, Ph.D. Principal Statistical Scientist, Biostatistics
Hina Patel, Pharm.D. Principal Safety Scientist, Safety Science

Alan Sandler, M.D. Principal Medical Director, Product Development Clinical Oncology
Daniel Waterkamp, M.D., Ph.D. Medical Director, Product Development Clinical Oncology
Jing Yi, Ph.D. Principal Statistical Scientist, Biostatistics
Fojan Zamanian Associate Program Director, Product Development Regulatory

Ventana

Julie Engel, Ph.D. Regulatory Affairs, Ventana Medical

1.0 BACKGROUND

On September 19, 2014, Genentech submitted a meeting request to discuss the proposed changes the ongoing studies GO28915 (OAK) and GO28754 (BIRCH) regarding the investigational product MDPL3280A.

MPDL3280A is a human (IgG₁ monoclonal antibody (mAb) consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), produced by recombinant DNA technology in Chinese hamster ovary cells. Genentech states that MPDL3280A binds to the human programmed death ligand 1 (PD-L1), thus inhibiting its interaction with its receptors, PD-1 and B7.1.

The purpose of this meeting is to seek feedback from the FDA regarding proposed changes to the definition of PD-L1-positivity in NSCLC patients and proposed modifications to the statistical analysis plans (i.e., modified hypothesis testing procedures) for the ongoing clinical studies OAK (GO28915) and BIRCH (GO28754). The external data supporting the proposed changes are summarized below.

Basis for proposed changes to BIRCH and OAK

Based on the observed results of exploratory analyses in single-arm trials conducted in the NSCLC cohort of the PCD4989g study and interim analyses of the FIR and POPLAR trials, respectively, Genentech has proposed revisions to the definition of PD-L1-positive NSCLC for the purpose of conducting a “prospective/retrospective” analysis of the BIRCH trial and a modification of the prospective efficacy analyses of the OAK trial and to submit the PMA for the PD-L1 companion diagnostic IHC assay in which the assay will assess PD-L1 in both tumor cells and in immune cells within tumor, using the tumor cell results for initial classification.

A summary of the clinical trial designs are shown in Table 2, abstracted from the meeting briefing package. Preliminary results of the ORR, PFS, and OS based on exploratory analyses of patient subsets defined by PD-L1-expression tumor profile supporting the proposed modifications for BIRCH and OAK are shown in Table 3.

Table 2. MPDL3280A monotherapy clinical trials in NSCLC

Study	Patient Population	Patients Planned (n)	Patients Enrolled (n)	MPDL3280A Dose	Randomized Controlled Design (Y/N)	Primary Endpoints	Purpose
PCD4989g (Phase I) ongoing	Incurable or refractory metastatic disease (NSCLC patients included)	656-689	461 ^a	WBD: 0.01 – 20 mg/kg q3w	N	Safety (DLTs), PK	Supportive Study
GO28625 (Phase II) (FIR) closed	Locally advanced or metastatic NSCLC	130	138 ^b	FD: 1200 mg q3w	N	ORR	Supportive Study
GO28753 (Phase II) (POPLAR) closed	Locally advanced or metastatic 2/3L NSCLC following progression of a platinum-containing regimen	300	287 ^b	FD: 1200 mg q3w	Y	OS for MPDL3280A vs. docetaxel	Supportive Study
GO28754 (Phase II) (BIRCH) ongoing	PD-L1–positive locally advanced or metastatic NSCLC	635	500 ^a	FD: 1200 mg q3w	N	ORR	Pivotal Study for Accelerated Approval
GO28915 (Phase III) (OAK) ongoing	NSCLC after failure with platinum-containing chemotherapy	1100	550 ^a	FD: 1200 mg q3w	Y	OS for MPDL3280A vs. docetaxel	Pivotal Study for Conversion to Full Approval

2L = second-line; 3L = third-line; DLT = dose-limiting toxicity; FD = fixed dosing; GCP = Good Clinical Practice; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; q3w = every 3 weeks; WBD = weight-based dosing.

Note: All clinical trials with MPDL3280A are conducted according to the principles of GCP.

^a Patients enrolled as of 9 October 2014.

^b Enrollment complete.

Table 3. Key efficacy results from Studies PCD4989g (NSCLC Cohort), FIR and POPLAR

	Study PCD4989g ^a	Study FIR ^b	Study POPLAR
ORR	50.0% (11/22)	30.0% (6/20)	39.1% (9/23)
"TC3 or IC3"	(95% CI: 28.2%, 71.8%)	(95% CI: 9.9, 50.1)	(95% CI: 19.2, 59.1)
PFS	30.7 weeks (median)	NR	HR=0.31
"TC3 or IC3"	(95% CI: 6, 73.1)		(95% CI: 0.13, 0.76)
OS	NA	NA	HR=0.52
"TC3 or IC3"			(95% CI: 0.15, 1.79)
ORR	31.6% (12/38)	17.3% (9/52)	25.0% (10/40)
"TC3 or IC2/3"	(95% CI: 17.5%, 48.6%)	(95% CI: 7.0, 27.6)	(95% CI: 11.6, 38.4)
PFS	12.0 weeks (median)	12 weeks (median)	HR=0.56
"TC3 or IC2/3"	(95% CI: 8.4, 44.0)	(95% CI: 6.0, 20.0)	(95% CI: 0.31, 1.01)
OS	NA	NA	HR=0.68
"TC3 or IC2/3"			(95% CI: 0.32, 1.45)

CI=confidence interval; HR=hazard ratio; IC=immune cell; NA=not available; NR=not reached;
NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival;
PFS=progression free survival; TC=tumor cell.

^a NSCLC cohort.

^b Cohort 2 (second-line patients).

BIRCH Trial Design

This is an ongoing multicenter single arm trial of PDL3280A in patients with PD-L1-positive (IHC 2+ or 3+), NSCLC. The protocol has undergone substantial revisions since the original version. The original version (version 1) of the protocol was finalized on August 22, 2013 and submitted to IND (b) (4) on October 1, 2013; version 2 is dated January 30, 2014; and version 3 is dated May 30, 2014. The description of the protocol below is based on Version 3.

Patients are being enrolled into the following 3 cohorts based on extent of prior therapy for NSCLC:

Cohort 1: Chemotherapy-naïve (first-line treatment with PDL3280A)

Cohort 2: One prior line of platinum-based chemotherapy (second-line treatment with PDL3280A)

Cohort 3: At least 2 lines of prior therapy (a platinum-based chemotherapy and at least one additional regimen for advanced NSCLC (third or greater line treatment with PDL3280A)

Patients with ALK and EGFR mutations can be enrolled in any Cohort after progression during or following treatment with appropriate tyrosine kinase therapy.

In all cohorts, MPDL3280A is administered at a fixed dose of 1200 mg intravenously on Day 1 of each 21-day cycle. In Cohort 1, patients may continue to receive MPDL3280A until RECIST-defined disease progression or unacceptable toxicity. For patients in Cohorts 2 and 3, patients may continue to receive MPDL3280A at the investigator's discretion as long as patients are demonstrating clinical benefit as assessed by the investigator defined as absence of unacceptable

toxicity or symptomatic deterioration attributed to disease progression. Tumor assessments are required at baseline and every 6 weeks thereafter for the first 12 months following Cycle 1, Day 1, with tumor assessments will be required every 9 weeks beyond month 12. Assessment of tumor status in patient ends treatment prior to disease progression regardless of whether patients start a new anti-cancer therapy until disease progression, withdrawal of consent, death, or study termination by Genentech.

The co-primary efficacy outcome measures are objective response rate (ORR), which is defined as the proportion of patients whose confirmed best overall response is either a partial response (PR) or a complete response (CR) based upon Independent Review Facility (IRF) assessment per RECIST v1.1 and investigator-determined ORR using modified RECIST criteria. Secondary efficacy outcome measures include IRF-assessed duration of response (DOR) per RECIST v1.1. The final analysis will be conducted when at least 254 patients have been enrolled in Cohort 3 and followed for 6 months or when at least 75 patients with IHC 3 PD-L1 expression have been enrolled in Cohort 3 and followed for 6 months, whichever occurs later.

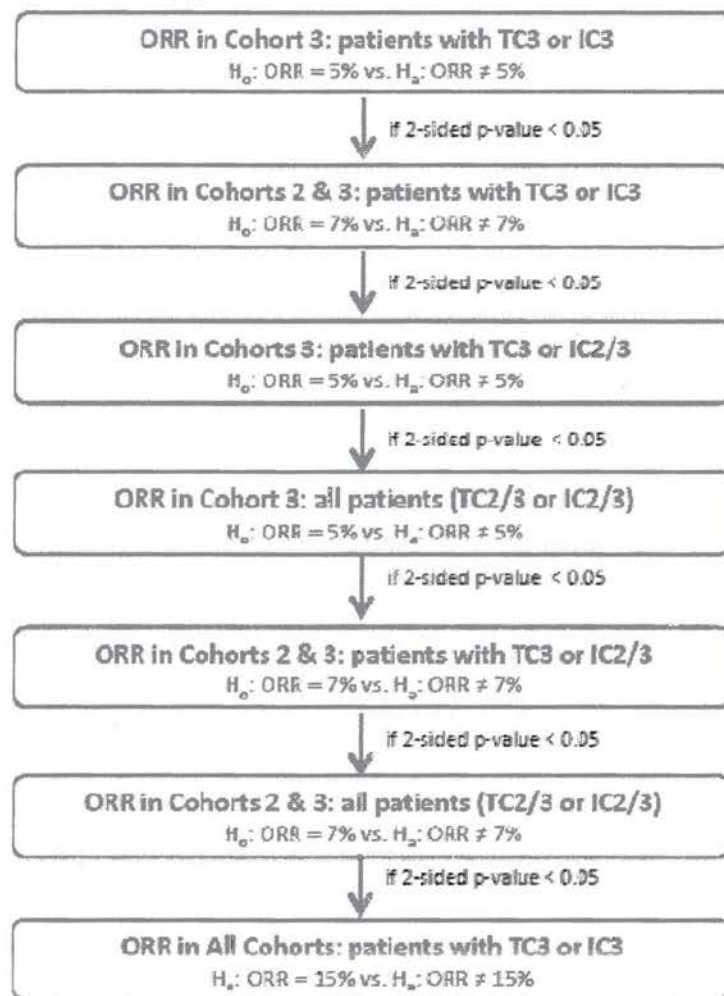
Proposed Revisions to BIRCH

The proposed changes are as follows:

- The number of patients needed for the final analysis of Cohort 3 would be increased from at least 75 patients with ICH 3 PD-L1 results to 100 patients with PD-L1 expression of "TC3 or IC3" in tumor specimens.
- The primary efficacy endpoint of ORR assessed by Investigator per modified RECIST v1.1 would be changed to a secondary efficacy endpoint.
- The statistical plan would be modified to reflect changes in the primary efficacy endpoint and the inclusion of PD-L1 expression in TC, in addition to IC, in the definition of PD-L1-positive NSCLC.
- Data obtained in patients with prospectively-identified PD-L1 positive tumors (IC2/3 as determined within 4 weeks of study enrollment) will be used in the pre-specified hierarchical analysis of the BIRCH study. Should the pre-specified hierarchical analysis of the "TC3 or IC2/3" subgroup demonstrate a statistically significant clinical benefit, Genentech proposes a plan to implement a bridging strategy (to be discussed with FDA at a future time) that may include generating IHC data through retrospective scoring of enrolled cases in the BIRCH study, according to the proposed testing procedure.

The following figure (Figure 1), abstracted from the meeting briefing document, illustrates Genentech's proposal for a revised hierarchical testing procedure for the data from BIRCH, based on a retrospective determination of TC scoring.

Figure 1. Hierarchical testing procedure in BIRCH



OAK Trial Design

This is an ongoing, multicenter, open-label, randomized, study designed to evaluate the efficacy and safety of MPDL3280A compared with docetaxel in patients with advanced NSCLC who have progressed during or following a platinum-containing regimen. Patients may have received no more than two prior regimens of cytotoxic chemotherapy treatment for their advanced NSCLC. Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory. Both patients and investigators will be blinded to the PD-L1 expression status. Eligibility requires tissue that is evaluable for expression testing prior to determination of PD-L1 expression status.

The randomization is stratified by PD-L1 IC status (four strata), by the number of prior chemotherapy regimens (1 versus 2), and by histology (non-squamous versus squamous), with equal allocation to one of the following treatment arms:

Experiment Arm: MPDL3280A at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day cycle.

Control Arm: Docetaxel 75 mg/m² will be administered intravenously on Day 1 of each 21-day cycle until disease progression per standard RECIST v1.1 or unacceptable toxicity.

The following criteria must be met for patients to continue MPDL3280A beyond RECIST v1.1-defined progressive disease:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Tumor assessments are required at baseline, at 6 weeks, and every 6 weeks (approximately every two cycles) thereafter for 36 weeks following randomization, then every 9 ($\pm$ 1) weeks. For patients randomized to MPDL3280A will undergo tumor assessments until disease progression per modified RECIST or until treatment discontinuation (for patients who continue to receive MPDL3280A following disease progression).

Safety assessments include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor MPDL3280A pharmacokinetics and to detect the presence of antibodies to MPDL3280A. Patient samples, including archival tumor tissues, as well as serum and plasma and whole blood, will be collected for future exploratory biomarker assessments.

The primary efficacy outcome measure for OAK is overall survival (OS). Secondary measures include progression free survival (PFS), ORR, and DOR. ORR is defined as the rate of patients with an unconfirmed objective tumor response (complete response [CR] or partial response [PR]) as determined by investigator using RECIST v1.1.

Proposed Revisions to OAK

A summary of the proposed changes are as follows:

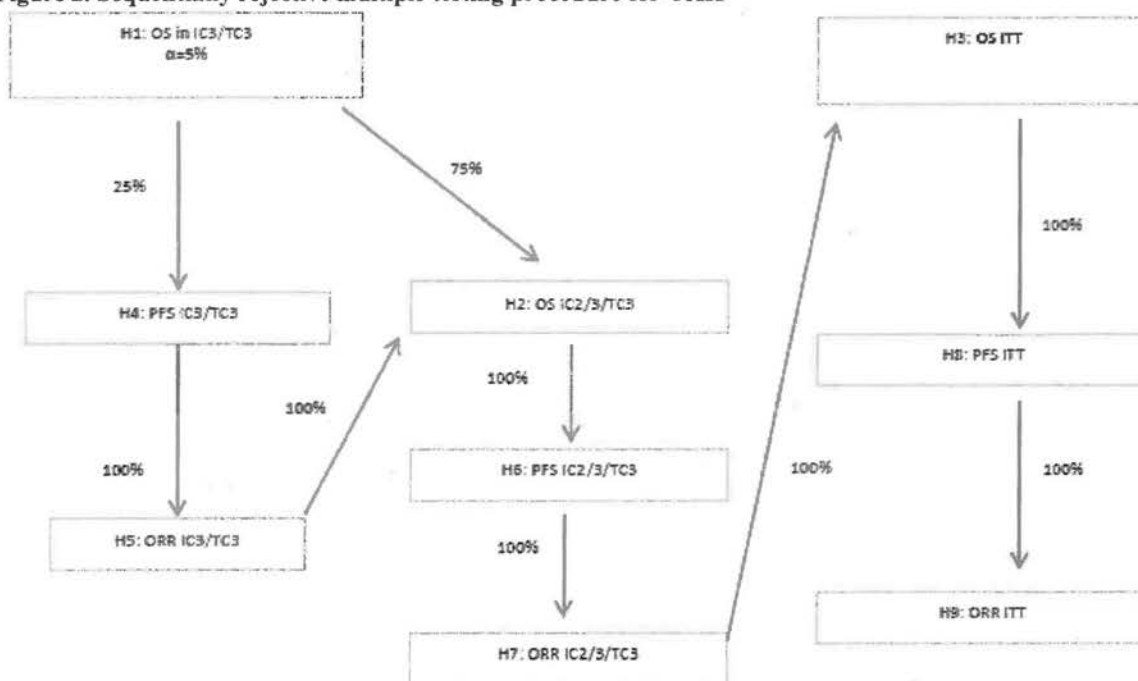
- The sample size would be increased from 850 to 1100 patients in order to ensure that at least 220 patients with PD-L1 TC3 or IC3 (assuming a prevalence of 20%) and approximately 330 patients with PD-L1 TC3 or IC2/3 (assuming a prevalence of 30%) will be enrolled.

- The statistical section would be amended to change the hypothesis testing procedures used to control the type I error (See Table 1 and Figure 2).
- The trial will be modified to consider PD-L1 expression in tumor or immune cells in the definition of PD-L1-positive NSCLC.

Table 1. Sample Size for Each Analysis Population

Analysis Population	Relative and Absolute OS Differences Targeted	Final analysis (# of deaths)	Alpha (2-sided)	Power	Sample Size
TC3 or IC3	HR=0.6 (median 8 vs.13.3 months)	170	5%	91.5%	220
TC3 or IC2/3	HR=0.68 (median 8 vs. 11.8 months)	264	3.75%	85.4%	330
ITT	HR=0.76 (median 8 vs. 10.5 months)	899	3.75%	97.7%	1100

Figure 2. Sequentially rejective multiple testing procedure for OAK



2.0 OBJECTIVES

- Agreement on conducting a retrospective re-analysis to identify a new diagnostic subgroup after enrollment or randomization, respectively, but prior to data analysis in the BIRCH and OAK studies.

- Agreement on the proposals to modify the hypothesis-testing procedures and increase the sample size in the OAK study.
- Agreement on the proposed modifications to modify the hypothesis-testing procedures in the BIRCH study.
- Agreement on the adaption of the statistical analysis plans and protocols for the OAK and BIRCH studies.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Study GO28754 (BIRCH)

1. Does the Agency agree that the first hierarchal testing on a pre-specified subgroup of patients with PD-L1 expression categorized as “TC3 or IC3” (see Table 2 for definitions) (b) (4) could enable registration of this PD-L1 selected population by accelerated approval under 21 CFR part 601, subpart E?

FDA Response: Yes, FDA agrees that demonstration of ORR of large magnitude and duration that provides substantial evidence of an effect (ORR) that it is reasonably likely to predict clinical benefit in patients with PD-L1 expression categorized as “TC3 or IC3” (b) (4) with a favorable benefit-risk profile, can potentially support accelerated approval of MPDL3280A under 21 CFR part 601, subpart E (b) (4). Please note that the exact indication will be determined at the time of review.

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency’s response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

2. Does the Agency agree that the Sponsor’s proposal to implement rescoring with the modified algorithm (TC3 reflex to IC3) on study BIRCH after enrollment and prior to final analysis would enable a PMA for this assay based upon these diagnostic criteria?

FDA Response: Patients were selected for analysis in the BIRCH study based on a PD-L1 IHC test result in tumor specimens of “TC2/3 or IC2/3”. Genentech proposes that tumor samples of all patients enrolled in study BIRCH will be retrospectively scored at a histopathology central testing lab using a modified scoring algorithm wherein samples are scored for TC3, and for below the TC3 cutoff, are subsequently tested for IC. Even though Genentech plans to implement the modified algorithm (TC3 followed by IC testing in TC negative samples) prior to the pre-specified BIRCH primary analysis, we have the following concerns:

- a. Clarify what “rescoring” means.
 - The proposed rescoring will be considered completely inappropriate if the laboratory receives any information about patient outcome and if a complete audit trail of the initial or subsequent scoring is not available for submission to FDA. It is not clear whether all the samples will be rescored again for the TC scoring and if the cases below TC3 will be scored for IC scoring and any samples with IC 3 will be in the analysis. This will change the ITT population. Please provide additional detail on initial scoring and plans for rescoring including what data is captured at both time-points.
 - Clarify whether Ventana can review the original readings and separate TC3 from TC2 cases (or IC3 from IC2) based on the staining intensity and percentage of each intensity level that were captured for TC and IC as part of the initial scores.
- b. Even if original readings included sufficient granularities (e.g., TC staining intensity and percentage of each intensity level, IC staining intensity and percentage of each intensity level) for the rescoring, FDA still has the following concerns:
 - Selection bias in the BIRCH study: Specifically, patients were initially selected for enrollment in the BIRCH study with $\geq 5\%$ tumor infiltrating immune cells (defined as IC) expressing PD-L1 (i.e., IC2/3) (denoted as part 1). The study protocol was later amended to also enroll patients with $\geq 5\%$ tumor cells (defined as TC) expressing PD-L1 (i.e., TC2/3) (denoted as part 2) based on emerging data from the Phase Ia study PCD4989g. It is conceivable that patients enrolled in Part 1 of the study may be different from those in Part 2 of the study. For instance, Part 1 of the BIRCH study enrolled patients with $\geq 5\%$ IC expressing PD-L1 (i.e., IC2/3), but excluded those patients with $< 5\%$ IC expressing PD-L1 (i.e., IC0/1), some of which may have $\geq 50\%$ TC expressing PD-L1 (i.e., TC3). As a result, this subgroup (i.e., TC3-IC0/1) may be under-represented in the BIRCH study and drug efficacy estimated from the trial for each subgroup defined in Figure 1 of page 19 could be potentially subject to bias. In order to have a better understanding of the clinical trial conduct and its impact on the study population Genentech should provide the following:
 - Clarification of how many patients are enrolled based on IC results only (i.e. what is part 1 sample size), and how many were based on TC and IC results (i.e. what is the part 2 sample size).
 - Distribution of IC subgroups for TC3 patients in BIRCH trial as compared that of the device’s intended use population and, if applicable, potential strategies to address the imbalance.

- c. Generally, the term “reflex testing” refers to testing performed on positive specimens to confirm diagnosis. Here “TC3 reflex to IC3” means samples are scored for TC3, and subsequently cases below the TC3 cutoff are scored for IC3. The use of the term “reflex” is confusing and therefore, CDRH recommends the sponsor change the wording “reflex” in “TC3 reflex to IC3” scoring algorithm.
- d. Analytical Validation: The device should be analytically validated using the new scoring criteria and satisfactory data provided in the PMA submission.

Genentech, Inc. December 9, 2014 Response 2a: The Sponsor acknowledges FDA’s comments and proposes that stained slides of all enrolled patients be retrospectively scored at a central testing lab using a modified algorithm wherein tissue samples are scored first for TC3, and subsequently, cases below the TC3 cutoff are scored for IC3 (i.e., TC3 reflex to IC3 algorithm). The central testing lab will not have access to any information about patient efficacy outcomes.

The Sponsor would additionally like to clarify the Agency’s expectations regarding the audit trail. Our interpretation is that the Agency would like documentation that the initial and subsequent scoring was conducted without any access to clinical outcome data.

Genentech seeks further clarity regarding what is meant by “this changes the ITT”. As the “TC3 or IC3” subgroup is identified among the patients enrolled per the criteria of IC2/3 or TC2/3, the Sponsor does not believe this changes the ITT population.

The Sponsor would like to clarify that staining intensity is not factored into the separation of TC3 from TC2 cases (or IC3 from IC2). Per the scoring criteria listed in Table 1 on pg. 14 of the Pre-meeting Package, a reader scores PD-L1 expression by the presence of discernible PD-L1 staining of any intensity. These criteria have been locked from the start of the study, and will be maintained through rescoring.

Discussion during the meeting: Genentech discussed the step-wise algorithm for rescoring patients’ tumor specimens from the BIRCH study. In collaboration with Ventana, Genentech will schedule a pre-Submission meeting with Center for Devices and Radiological Health (CDRH) and will present validation plans on the TC3 and IC3 cut-offs. FDA agreed with this approach. Genentech confirmed that there will be a prospective-retrospective (i.e., performed prior to analysis of patient outcomes) rescoring of slides based on the new scoring algorithm (TC3 or IC3) for PD-L1 positivity.

FDA confirmed that Genentech’s interpretation of the audit plan as outlined in their response is acceptable. Genentech will cross-reference the information on the data access control plan submitted to IND 117296 at the time of BLA submission. Genentech confirmed that the central pathologic readers for the rescoring are blinded to clinical outcome data and previous scoring.

FDA agrees that the rescoring of samples will not impact the ITT population in BIRCH, which remains unchanged and is defined as all patients with prospectively-identified PD-L1 positive tumors (IC2/3 as determined within 4 weeks of study enrollment).

FDA acknowledges Genentech's responses regarding staining intensity.

Genentech, Inc. December 9, 2014 Response 2b: Genentech acknowledges the Agency's response. The IDE was amended in July 2014. Prior to this amendment, we had enrolled 161 patients based on IC2/3. These patients represent ~25% of all BIRCH patients (n=667). The remaining 506 patients were enrolled after the IDE amendment, based on TC2/3 or IC2/3.

Our preliminary estimates of the IC distribution subgroups for TC3 patients are comparable between enrolled and screened populations at this time. However, if imbalances do appear, sensitivity analyses will be performed.

Discussion during the meeting: In the BLA submission, FDA requested that Genentech provide a description of the baseline characteristics of patients enrolled on BIRCH before and after the July 2014 IDE amendment.

FDA agrees that if imbalances of the IC distribution subgroups for TC3 patients between enrolled and screened populations do appear, sensitivity analyses should be performed and submitted to the BLA.

Genentech, Inc. December 9, 2014 Response 2c: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Genentech, Inc. December 9, 2014 Response 2d: The IVD Sponsor (Ventana Medical Systems) commits to providing analytic validation data for the new scoring criteria in the PMA submission. No further clarification is needed during the meeting.

Discussion during the meeting for 2c and 2d: No discussion occurred during the meeting for 2c and 2d.

3. Does the Agency agree that a subsequent pre-specified analysis of data from the "TC3 or IC2/3" (b)(4) could enable registration of this PD-L1 selected population by accelerated approval under 21 CFR part 601, subpart E?

FDA Response: Yes, FDA agrees that demonstration of ORR of a magnitude and duration that provides substantial evidence of an effect that it is reasonably likely to predict clinical benefit in patients with PD-L1 expression categorized as "TC3 or IC2/3" (b)(4) accompanied by a favorable benefit-risk profile can potentially support accelerated approval of MPDL3280A under 21 CFR part 601, subpart E (b)(4). Please note that this proposed broader indication, "TC3 or IC2/3", would not be granted if the results are solely driven by a subgroup of patients (e.g., "TC3 or IC3").

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

4. Does the Agency agree that the Sponsor's proposal to implement a bridging strategy for the modified scoring algorithm of "TC3 reflex to IC2" after final analysis of study BIRCH could enable a PMA for this assay?

FDA Response: Genentech's plan to seek a PMA supported by retrospective scoring of enrolled cases in the BIRCH study using the new ("TC3 reflex to IC2") testing algorithm appears reasonable if the pre-specified hierarchical analysis of the "TC3 or IC2/3" subgroup demonstrates an effect on ORR that is large in magnitude and a duration of response that is clinically meaningful.

The bridging strategy includes generating new IHC results through retrospective scoring of patients' tumor specimens from the BIRCH study, using the "TC3 reflex to IC2" algorithm, if the pre-specified hierarchical analysis of the "TC3 or IC 2/3 subgroup" demonstrates an effect that could support a request for accelerated approval (for MPDL3280A. FDA recommends that Ventana change the algorithm and perform the scoring prior to the analysis. Please note that PMA approval is contingent on demonstration of a durable and large magnitude of ORR in BIRCH in the planned hierarchical testing procedure. Also, as stated above, approval for a proposed broader intended use (i.e., to identify patients with PD-L1-positive NSCLC, defined as TC3 or IC2/3, would not be granted if the results are solely driven by a subgroup of patients (e.g., "TC3 or IC3").

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

5. Does the Agency agree with the proposed changes to the statistical analysis in the protocol and statistical analysis plan (SAP) (including the modification plan) for study BIRCH?

FDA Response: The proposed changes appear acceptable.

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

Study GO28915 (OAK)

6. The OAK study is currently stratified by four IC levels (IC0, IC1, IC2 and IC3; see Table 2). Based on emerging data from three independent studies, the Phase Ia study PCD4989g, the Phase II study FIR and the randomized Phase II study POPLAR demonstrating clinical benefit in patients with “TC3 or IC3”, the Sponsor proposes to include TC3 as a component of the definitions of PD-L1 selected subgroups that will be analyzed. The Sponsor proposes to increase the sample size of study OAK to enable a modification of the hypothesis testing to include pre-specified, statistically powered analyses of subgroups of patients with tumors that are “TC3 or IC3” and patients with tumors that are “TC3 or IC2/3”. The Sponsor plans to utilize the PMA from BIRCH for the PD-L1 diagnostic IHC assay with the TC3 reflex to IC3 scoring algorithm. Tumor samples will be retrospectively scored as “TC3 or IC3” using the “TC3 reflex to IC3” algorithm, prior to pre-specified analysis. The “TC3 or IC2/3” subgroup will include patients with “TC3 or IC3” and patients with IC2/3 (i.e., at or above the IC2 cutoff) identified from the initial stratification. If pre-specified analysis of the “TC3 or IC2/3” subgroup demonstrates a statistically significant clinical benefit, the Sponsor proposes to implement an analytic bridging strategy for a “TC3 reflex to IC2” algorithm.

Does the Agency agree that the first hierarchical testing on a pre-specified subgroup of patients with PD-L1 expression categorized as “TC3 or IC3” could enable labeling and conversion to full approval for this PD-L1 selected population?

FDA Response: Yes, FDA agrees that demonstration of a highly statistically significant prolongation of overall survival that provides substantial evidence of effectiveness and an acceptable benefit-risk profile in patients with metastatic NSCLC with PD-L1 expression categorized as “TC3 or IC3” in OAK can potentially support traditional approval of MPDL3280A. Please note that the exact indication will be determined at the time of review.

Given that patients in OAK were stratified only by IC level and thus the proposed analysis will not be conducted in the “as randomized” population, Genentech should discuss their evaluation for and impact of potential biases that may exist that result from lack of randomization in the BLA submission.

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency’s response and will evaluate the impact of potential bias in the OAK BLA submission. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

7. Does the Agency agree that a subsequent pre-specified analysis of data from the “TC3 or IC2/3” subgroup could enable labeling and conversion to full approval for this PD-L1 selected population?

FDA Response: Yes, FDA agrees that demonstration of a highly statistically significant prolongation of overall survival that provides substantial evidence of effectiveness with an acceptable benefit-risk profile in patients with metastatic NSCLC categorized as PD-L1-positive, i.e., “TC3 or IC2/3”, following rejection of the H1 null hypothesis in OAK can potentially support traditional approval of MPDL3280A. Please note that this proposed broader indication, “TC3 or IC2/3”, would not be granted if the results are solely driven by a subgroup of patients (e.g., “TC3 or IC3”). See FDA’s response to question # 9.

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency’s response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

8. Does the Agency agree that the Sponsor’s proposal to implement a bridging strategy for a “TC3 reflex to IC2” algorithm after final analysis of study OAK could enable a PMA for this assay?

FDA Response: If the investigational drug, MPDL3280A, is granted accelerated approval based on the BIRCH trial with a contemporaneous approval of the device, then a new PMA for the OAK trial may not be required. Please see FDA’s response to question # 9 which also applies to the analysis of data supporting the PMA.

Genentech, Inc. December 9, 2014 Response: Genentech acknowledges the Agency’s response. No further clarification is needed during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

9. Does the Agency agree with the amended SAP (including modification plan) for study OAK?

FDA Response: In general, the amended SAP appears acceptable. However, FDA has the following comments:

- a. The proposed analysis populations based on both TC and IC categories may support the primary analyses. Please note that the possible imbalance in baseline prognostic factors between the two arms will be a review issue.
- b. The sequentially rejective multiple test approach is acceptable to control the overall Type I error rate. However, positive results in the intent-to-treat (ITT) population might be driven by positive results of a subgroup with “TC3 or IC3” or “TC3 or IC2/3”. Similarly, positive results of the subgroup with “TC3 or IC2/3” might be driven by positive results of a subgroup with “TC3 or IC3”. The interpretation of analysis results will be considered in light of the treatment effect in complimentary subgroups.

- c. Genentech should include a detailed plan for the PFS censoring rules in the SAP.
- d. If Genentech intends to make a labeling claim based on durable ORR, the responses (complete response and partial response) must be confirmed.

Genentech, Inc. December 9, 2014 Response 9a: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Genentech, Inc. December 9, 2014 Response 9b: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Genentech, Inc. December 9, 2014 Response 9c: Genentech acknowledges the Agency's response and will include a detailed plan for PFS censoring rules in the SAP. No further clarification is needed during the meeting.

Genentech, Inc. December 9, 2014 Response 9d: Genentech acknowledges the Agency's response. No further clarification is needed during the meeting.

Discussion during the meeting for 9a, 9b, 9c, and 9d: No discussion occurred during the meeting for 9a, 9b, 9c, and 9d.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. We further note that an End-of-Phase 2 meeting was held on October 22, 2013, and your iPSP submitted on April 15, 2014, is currently under review.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical

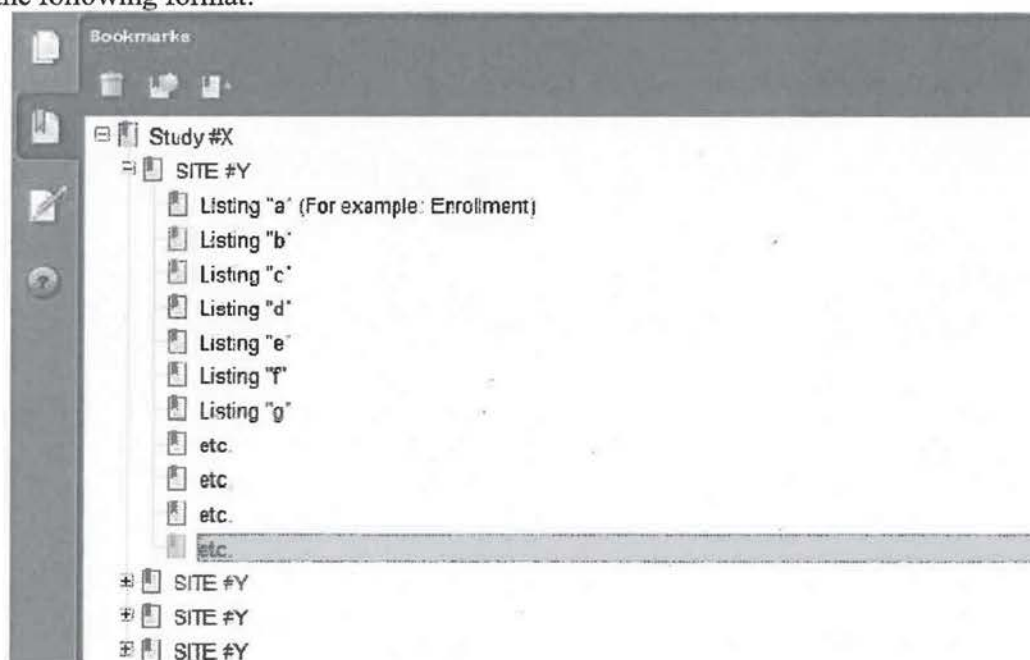
investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates

- g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```

- [m5]
  - datasets
    - bimo
      - site-level

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- C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

RUTH L MADURO
01/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Fojan Zamanian
Regulatory Health Project Management
1 DNA Way MS#214B
South San Francisco, CA 94080-4990

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 the meeting between representatives of your firm and the FDA on October 22, 2013. The purpose of the meeting was to discuss the proposed phase 2 study (Study GO28754), intended to support accelerated approval and the proposed phase 3 study (Study GO28915), intended to support conversion to full approval.

A copy of the official minutes of the meeting 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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B Meeting
Meeting Category: End of Phase 2
Meeting Date and Time: Tuesday, October 22, 2013
Meeting Location: 12:00 PM – 1:00 PM
Application Number: IND 117296
Product Name: MPDL3280A
Indication: NSCLC
Sponsor/Applicant Name: Genentech, Inc.
Meeting Chair: Gideon Blumenthal
Meeting Recorder: Gina Davis

FDA ATTENDEES

Center for Drug Evaluation and Research

Office of Hematology and Oncology Products

Division of Oncology Products 2

Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2)
Joseph Gootenberg, M.D. Deputy Director, DOP 2
Gideon Blumenthal, M.D., Medical Team Lead, DOP 2
Sean Khozin, M.D., Medical Officer, DOP 2
Lee Pai-Scherf, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Health Project Manager, DOP 2

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Stacy Shord, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology V

Office of Biostatistics

Division of Biostatistics V

Shenghui Tang, Ph.D., Statistical Team Lead, Division of Biometrics V (DB V)
Stella Karuri, Ph.D., Statistics Reviewer, DB V

Office of Biotechnology Products

Division of Monoclonal Antibodies

Laurie Graham, Ph.D., Supervisor, Division of Monoclonal Antibodies

Center for Devices and Radiologic Health

Office of In Vitro Diagnostics

Division of Immunology and Hematology Devices

Yun-Fu Hu, Ph.D., Branch Chief, Division of Immunology and Hematology Devices (DIHD)
Shyam Kalavar, MPH, CT (ASCP), Diagnostics Device Reviewer, DIHD

SPONSOR ATTENDEES

Genentech, Inc.

Cathi Ahearn Lifecycle Team Leader, Global Product Strategy Oncology
Anna Beryozkina, Pharm.D., Associate Program Manager, Product Development Regulatory
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
Daniel Chen, M.D., Ph.D. Associate Group Director, Product Development Clinical
Oncology
Marcin Kowanetz, Ph.D. Scientist, Oncology Biomarker Development
Ben Lyons, Ph.D. Associate Director, Biostatistics
Ahmad Mokatrín, Ph.D. Principal Statistical Scientist, Biostatistics
Alan Sandler, M.D. Principal Medical Director, Product Development Clinical
Oncology
Jing Yi, Ph.D. Senior Statistical Scientist, Biostatistics
Daniel Waterkamp, M.D., Ph.D., Medical Director, Product Development Clinical Oncology
Fojan Zamanian Associate Program Director, Product Development Regulatory

Ventana

Brian Baker Regulatory Affairs, Ventana Medical Systems

1.0 BACKGROUND

On August 14, 2013, Genentech Inc. (Genentech) submitted a meeting request to discuss the following proposed clinical trials with the investigational product MPDL3280A for the treatment of advanced non-small cell lung cancer (NSCLC) after failure of a platinum-containing chemotherapy regimen:

- Phase 2 Study GO28754 - BIRCH – “A single-arm trial in NSCLC (all lines of therapy including treatment naïve) selected on the basis of PD-L1-positive tumor status using a PD-L1 immunohistochemistry (ICH) assay” intended to support accelerated approval
- Phase 3 Study GO28915- OAK – “Randomized Trial in second-or third-Line, PD-L1-positive and negative NSCLC patients stratified by PD-L1 tumor status using a PD-L1 IHC assay” intended to support conversion to full approval

Genentech states that 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 (b) (4)

. MPDL3280A targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1, both of which can provide inhibitory signals to T cells.

Genentech states that MPDL3280A is administered at a fixed dose of 1200 mg (equivalent to an average bodyweight-based dose of 15 mg/kg) by an intravenous (IV) infusion every 3 weeks (21 days) for up to 16 cycles (or 1 year, whichever comes first).

The proposed clinical development of MDPL32850A for the treatment of NSCLC is shown in Table 1. Study GO28754 (BIRCH) is a single arm trial serving as the primary source of data for potential accelerated approval and will enroll patients with PD-L1-positive tumors defined as IHC 2+ and 3+ (Table 2). Study GO28625 (FIR) is a single arm trial that will enroll locally advanced or metastatic NSCLC patients with PD-L1-positive tumors. Study GO28753 (POPLAR) is a randomized trial with MPDL3280A vs. docetaxel in second-line/third-line NSCLC patients stratified by PD-L1 tumor status (IHC 0, IHC 1, IHC 2, and IHC 3) with a primary endpoint of overall survival (OS). Study GO28915 (OAK) is a randomized trial in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. Genentech intends to use this trial as the basis for potential conversion to regular approval. Approximately 850 eligible patients will be stratified by PD-L1 IHC status (four categories of PD-L1 expression), by the number of prior chemotherapy regimens (1 versus 2), and by histology (non-squamous versus squamous) and then randomized 1:1 to receive either MPDL3280A or docetaxel. The primary endpoint of the trial is OS. BIRCH uses a hierarchical statistical plan where 3 tests will be performed sequentially on the investigator-assessed ORR according to modified RECIST and on the IRF-assessed ORR according to RECIST v1.1. Genentech presents the hierarchical procedure as follows:

1. Test investigator-assessed ORR per modified RECIST in patients treated in Cohort 3 (third-line + patients) vs. null hypothesis (Ho) of 5%.
2. Test ORR by IRF per RECIST v1.1 in patients treated in Cohort 3 (third-line + patients) vs. null hypothesis (Ho) of 5%.
3. Test investigator-assessed ORR per modified RECIST in all treated patients with PD- L1 IHC 3+ vs. null hypothesis (Ho) of 15%.
4. Test ORR by IRF per RECIST v1.1 in all treated patients with PD-L1 IHC 3+ vs. null hypothesis (Ho) of 15%.
5. Test investigator-assessed ORR per modified RECIST in all treated patients vs. null hypothesis (Ho) of 15%
6. Test ORR by IRF per RECIST v1.1 in all treated patients vs. null hypothesis (Ho) of 15%.

In OAK, Genentech states that comparisons with respect to the OS between the treatment arms within each subgroup defined by the PD-L1 IHC strata will be tested using a hierarchical fixed-sequence procedure as follows:

1. First, test to reject the null hypothesis of no difference in OS between the two arms in the group of patients with IHC 2/3+. If the p-value corresponding to the stratified, two-sided log-rank test is $< 5\%$, the null hypothesis will be rejected, and it will be concluded that MPDL3280A prolongs the duration of OS relative to docetaxel in the IHC 2/3+ subpopulation.
2. If the null hypothesis from Step 1 is rejected, then test to reject the null hypothesis of no difference in OS between the two arms in the group of patients with IHC 1/2/3+. If the p-value corresponding to the stratified, two-sided log-rank test is $< 5\%$, the null hypothesis will be rejected, and it will be concluded that MPDL3280A prolongs the duration of OS relative to docetaxel in the IHC 1/2/3+ subpopulation.
3. If the null hypothesis from Step 2 is rejected, then test the null hypothesis of no difference in OS between the two arms in the overall population (i.e., the intent-to-treat [ITT] patients or those with IHC 0/1/2/3). If the p-value corresponding to the stratified, two-sided log-rank test is $< 5\%$, the null hypothesis will be rejected, and it will be concluded that MPDL3280A prolongs the duration of OS relative to docetaxel in the overall population.

If the primary endpoint of OS is statistically significant at the 5% level (two-sided) in the overall population (i.e., ITT patients with IHC 0/1/2/3), Genentech will test the secondary endpoint of ORR in the three populations specified, using the same hierarchical fixed-sequence method as for OS. If the secondary endpoint of ORR is statistically significant at the 5% level (two-sided) in the overall population (i.e., ITT patients with IHC 0/1/2/3), the secondary endpoint of PFS will be tested in the three subgroups of IHC using the same hierarchical fixed-sequence method as for OS.

Table 1. Proposed clinical development for MDPL32850A

Study (Projected Initiation)	Tumor Status	Study Design	CDx Assay	Regulatory Purpose
GO28625 (FIR) (ongoing)	PD-L1 positive	• Single arm, Phase II • Patient population (n = 130): – Metastatic or locally advanced NSCLC – ECOG PS 0–1 – 1L approximately 45 patients – 2L+ approximately 75 patients – CNS metastases approximately 10 patients • Dose: MPDL3280A as a fixed dose of 1200 mg IV q3w × 16 cycles • 1° endpoint: ORR per modified RECIST	Validated IUO-labeled prototype IHC assay	Supportive study for accelerated approval of MPDL3280A
GO28754 (BIRCH) (Q4 2013)	PD-L1 positive	• Single arm, Phase II • Patient population (n = 300): – Metastatic or locally advanced NSCLC – ECOG PS 0–1	IUO-labeled, design-locked IHC assay	Pivotal study for accelerated

Study (Projected Initiation)	Tumor Status	Study Design	CDx Assay	Regulatory Purpose
		– 1L approximately 70 patients 2L approximately 80 patients 3L+ at least 150 patients • Dose: MPDL3280A as a fixed dose of 1200 mg IV q3w × 16 cycles • Co-primary endpoints: ORR per modified RECIST and ORR per RECIST v1.1		approval of MPDL3280A
GO28753 (POPLAR) (ongoing)	PD-L1 positive or negative	• Randomized Phase II, MPDL3280A vs. docetaxel • Patient population (n = 180): – Metastatic or locally advanced NSCLC – Stratified by diagnostic status and other baseline prognostic factors – ECOG PS 0–1 – 2L/3L • Dose: MPDL3280A as a fixed dose of 1200 mg IV q3w × 16 cycles • 1° endpoint: OS	Validated IUO-labeled prototype IHC assay	Supportive study for accelerated approval of MPDL3280A

Study (Projected Initiation)	Tumor Status	Study Design	CDx Assay	Regulatory Purpose
GO28915 (OAK) (Q1 2014)	PD-L1 positive or negative	• Randomized Phase III, MPDL3280A vs. docetaxel • Patient population (n = 850): – Metastatic or locally advanced NSCLC – Stratified by diagnostic status and other baseline prognostic factors – ECOG PS 0–1 – 2L/3L • Dose: MPDL3280A as a fixed dose of 1200 mg IV q3w × 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 procedure)	IUO-labeled, design-locked IHC assay	Proposed study for conversion to full approval of MPDL3280A

1L=first-line; 2L=second-line; 3L=third-line; CDx=companion diagnostic; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; IHC=immunohistochemistry; IUO=investigational use only; IV=intravenous; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death–ligand 1; PS=performance status; q3w=once every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.

Genentech is proposing a development plan in which an investigational use only (IUO) device currently under IDE utilized in Study GO28754 (BIRCH) and Study GO28915 (OAK) to select patients enrolled into Study GO28625 (FIR) and to stratify patients in Study GO28753

(POPLAR). A “design-locked,” IUO-labeled IHC assay will be used to select patients for enrollment into Study GO28754 (BIRCH) and to stratify patients in Study GO28915 (OAK). According to Genentech, a retrospective analysis of PD-L1 expression by IHC in tumor specimens obtained from patients who received MPDL3280A in an ongoing study (PCD4989g) was used to determine the PD-L1 diagnostic threshold for clinical benefit.

Table 2. Proposed Criteria for PD-L1 Diagnostic Assessment in Studies GO28915 (OAK) and GO28754 (BIRCH)

Diagnostic Assessment for Study GO28754 (BIRCH)	Description of IHC Scoring Algorithm	Diagnostic Assessment for Study GO28915 (OAK)
Negative	Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IHC 0
	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering between $\geq 1\%$ to < 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IHC 1
Positive	Presence of discernible PD-L1 staining of any intensity in tumor infiltrating immune cells covering between $\geq 5\%$ to < 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IHC 2
	Presence of discernible PD-L1 staining of any intensity in tumor infiltrating immune cells covering $\geq 10\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IHC 3

IHC = immunohistochemistry; PD-L1 = programmed death–ligand 1.

Data from GO28625 (FIR) and GO28753 (POPLAR) will be used to modify the analysis plan for Study GO28754 (BIRCH). The proposed modification would be triggered by observation of superior efficacy in the IHC 3+ cohorts in FIR and POPLAR and would involve modification of hierarchical testing procedures so that ORR in the 3L+ subpopulation is tested first (Table 3).

Table 3. Potential Modification Scenario in BIRCH

Scenarios	Observation	Modification
Efficacy pronounced in PD-L1 IHC 3 patients: Test PD-L1 IHC 3 first.	Data from FIR and POPLAR indicate that response rates and other efficacy parameters in the IHC 3 population are substantially superior to those in the IHC 2 and IHC3 population.	Modify hierarchical testing in BIRCH so that the ORR in the 3L+ patients with PD-L1 IHC 3 subpopulation will be tested first.

Notes: Study GO28754 = BIRCH; Study GO28625 = FIR;
Study GO28753 = POPLAR.

3L = third-line; IHC = immunohistochemistry; ORR = objective response rate;
PD-L1 = programmed death–ligand 1.

Data from Study GO28753 (POPLAR) will be used to modify the analysis plan for Study GO28915 (OAK), the study proposed for conversion to regular approval (Table 4). The potential modifications include changing the order of endpoints so that ORR and PFS in IHC 2/3+ subpopulations will be tested after OS is tested in IHC 2/3+ and before OS test in the 1/2/3+ and ITT populations.

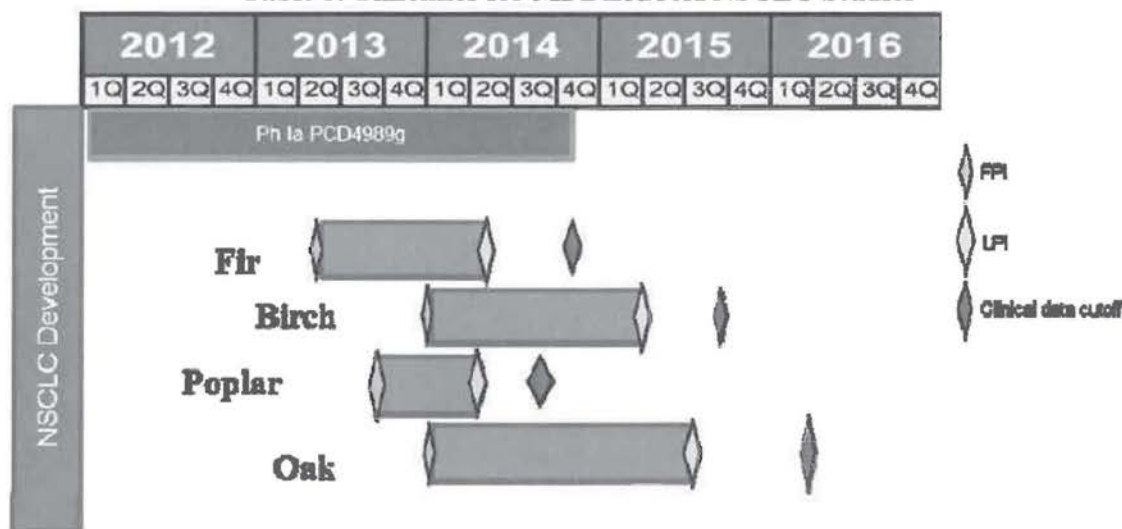
Table 4. Potential Modification Scenarios in OAK

Scenarios	Observation	Modification
Lack of predictive effect of IHC status: Test ITT population (IHC 0/1/2/3) first.	Evidence of substantial and consistent treatment effect across all diagnostic strata in the ITT population in POPLAR	Modify testing of the hierarchy of OAK so that OS (followed by ORR and PFS) in the ITT population will be tested first.
Delayed treatment effect	Evidence of delayed treatment effect in POPLAR (non-proportional hazards)	Increase follow-up duration in OAK.
Stronger treatment effect limited to IHC 2/3 on all endpoints	Evidence of substantially stronger treatment effect in the IHC 2/3 subpopulation relative to the ITT or IHC 1/2/3 subpopulations in POPLAR	Modify order of endpoints in OAK so that ORR in IHC 2/3 subpopulation and PFS in IHC 2/3 subpopulation will be tested after OS is tested in IHC 2/3 subpopulation and before OS test in the IHC 1/2/3 subgroup and ITT population.
Stronger treatment effect	Evidence of strong treatment effect in the IHC 2/3, IHC 1/2/3, and ITT populations in POPLAR	Decrease the follow-up duration in OAK for all patients.

Notes: Study GO28754=BIRCH; Study GO28625=FIR; Study GO28753=POPLAR.
3L=third-line; IHC=immunohistochemistry; ITT=intent to treat; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival.

The timing of the proposed clinical trials is shown in Table 5.

Table 5. Timelines for MPDL3280A NSCLC Studies



2L=second-line; doc=docetaxel; Dx=diagnostic; FPI=first patient in; LPI=last patient in; NSCLC=non-small cell lung cancer.
Notes: Study GO28625 (FIR): FPI=May 2013; LPI=April 2014; primary analysis clinical data cutoff=October 2014.
GO28754 (BIRCH): FPI=December 2013; LPI=March 2015; primary analysis clinical data cutoff=September 2015.
GO28753 (POPLAR): FPI=August 2013; LPI=March 2014; primary analysis clinical data cutoff=August 2014.
GO28915 (OAK): FPI=January 2014; LPI=June 2015; primary analysis clinical data cutoff=April 2016.

2.0 OBJECTIVE

- to discuss and to obtain agreement on the acceptability of the protocols and analysis plans for Studies GO28754 (BIRCH) and GO28915 (OAK) in order to support approval of MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC that is programmed death-ligand 1 (PD-L1) positive, as determined by an FDA-approved test, after failure of a platinum-containing chemotherapy regimen.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

QUESTIONS

PREAMBLE: In the Type C meeting package dated April 26, 2013, Genentech indicated that the FIR and POPLAR trials would be initiated using material manufactured with "Process 1" while the OAK and BIRCH trials would use material produced from a new manufacturing process, "Process 3". Please note, the information on Process 3, received in an amendment dated October 1, 2013, has not yet been reviewed. The following advice is provided under the assumption that materials produced by Process 1 and Process 3 are comparable.

- The Phase II, single-arm Study GO28754 (BIRCH) will enroll patients with PD-L1-positive tumors as defined by IHC 2+ and 3+ (see Section 8.1 and Table 7). An IDE application for BIRCH will be submitted describing the verification for the IHC assay

and ICH 2+ scoring algorithm prior to study initiation. Verification of IHC 3+ will be completed prior to the pre-specified BIRCH primary analysis.

A Phase II, single-arm Study GO28625 (FIR) will enroll locally advanced or metastatic NSCLC patients with PD-L1-positive tumors with scoring algorithm IHC 2+. A Phase II, Study GO28753 (POPLAR) in second-line/third-line NSCLC patients stratified by PD-L1 tumor status using the PD-L1 IHC assay will be performed to assess the treatment effect of MPDL3280A in second-line/third-line NSCLC and to evaluate efficacy in the populations as defined by scoring algorithms IHC 0+, IHC 1+, IHC 2+, and IHC 3+ (see Section 8.1 and Table 7). Data from FIR and POPLAR will be used to determine if the pre-specified analyses used in BIRCH are appropriate or if they should be modified.

Does the Agency agree with the proposed hierarchal testing plan for BIRCH?

FDA response: FDA does not object to the concept of hierarchal testing for BIRCH. As currently designed, the BIRCH trial is not adequate to support a claim for accelerated approval of MDL3280A for the treatment of advanced NSCLC patients for whom available therapy provides an improvement in OS.

The proposed primary analysis conducted in modified RECIST is unacceptable to support labeling claims. Instead, ORR per RECIST v1.1 should be the first test rather than ORR by modified RECIST as there is insufficient experience with ORR by modified RECIST to determine whether it may be a surrogate for clinical benefit, which would preclude a determination that a large treatment effect on ORR by modified RECIST observed in this trial provides a substantial improvement over available therapy that is reasonably likely to predict clinical benefit.

Please note that for a single arm study, a request for approval based on ORR needs to be supported by ORR of sufficient magnitude and duration to be likely to predict clinical benefit, as well as an acceptable risk/benefit ratio.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question # 1: We acknowledge FDA's comment. We plan to amend the protocol for the hierarchical testing procedure for ORR.

The hierarchical procedure in the protocol will be modified as follows:

- Test ORR by IRF per RECIST v1.1 in patients treated in Cohort 3 vs. null hypothesis (Ho) of 5%, then
- Test investigator-assessed ORR per modified RECIST in patients treated in Cohort 3 vs. null hypothesis (Ho) of 5%, then
- Test ORR by IRF per RECIST v1.1 in patients with IHC 3 and treated in all three cohorts vs. null hypothesis (Ho) of 15%, then

- Test investigator-assessed ORR per modified RECIST in patients with IHC 3 and treated in all three cohorts vs. null hypothesis (Ho) of 15%, then
- Test ORR by IRF per RECIST v1.1 in all treated patients vs. null hypothesis (Ho) of 15%, then
- Test investigator-assessed ORR per modified RECIST in all treated patients vs. null hypothesis (Ho) of 15%

Discussion during the meeting: FDA does not object to the Genentech's October 21, 2013, proposal for hierarchical testing; however the criteria for accelerated approval remain as stated above (see comment below).

"Please note that for a single arm study, a request for approval based on ORR needs to be supported by ORR of sufficient magnitude and duration to be likely to predict clinical benefit, as well as an acceptable risk/benefit ratio."

2. Does the Agency agree with the plans proposed by the Sponsor to alter the analysis plan for BIRCH if supported by data from FIR and POPLAR?

FDA response: Yes, Genentech's proposal appears acceptable provided that the changes made are entirely based on the external data and that Genentech remains blinded to the results of BIRCH. Also see response to Question 1.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question # 2: In the Agency's response to Questions 2 and 5 it states that Genentech's proposals appear acceptable provided that the changes made are entirely based on the external data and that Genentech remains blinded to the results of BIRCH/OAK. Genentech would like to clarify the following points regarding the conduct of BIRCH and OAK:

Population Level Data Summary:

- Genentech will remain blinded to the results of BIRCH and OAK (i.e. the population level efficacy data summaries) until the primary analysis.

Individual Patient Level Data:

- Genentech will remain blinded to patient PD-L1 IHC status for the BIRCH or OAK studies. Genentech will also remain blinded to treatment randomization assignment in the OAK study, with the only exception being patients who have serious adverse events as outlined in Genentech's internal SOPs.
- There will be a limited number of individuals on the study team at Genentech who will have access to patient level data, exclusive of patient PD-L1 IHC status (BIRCH and OAK) and treatment randomization assignment (OAK), e.g. data management and site monitors. However, these individuals with access to patient level data will be prohibited from conducting population level data summaries.

Communication of clinical data between these individuals and others within Genentech will be strictly controlled and tracked.

- Separate Genentech teams that are independent of the study teams for BIRCH and OAK will only have access to the individual efficacy data in order to issue queries for data cleaning purposes. Efficacy data includes all tumor assessments and survival related data (i.e. treatment and study discontinuation and survival follow up data). Please Note: these individuals will not produce population level efficacy data summaries and will not have input on any modification to the BIRCH or OAK study. For OAK, this team will not have access to the treatment administration and randomization code. Communication between this separate team and others will be strictly controlled and tracked.

Discussion during the meeting: FDA acknowledged Genentech's clarifications and stated that all concerns were addressed regarding external data. In addition, FDA agreed that, based on the timelines provided in the attached slides, there will be adequate time for FDA review of external data from FIR and POPLAR trials prior to the data cut-off for BIRCH.

3. Given that BIRCH will enroll patients with IHC $\geq 2+$, and design verification of IHC 3+ will be completed prior to the primary analysis of BIRCH and not prior to the start of the study, does the Agency agree that data from BIRCH based on IHC 2+ and/or IHC 3+ cutoffs could support a BLA filing and accelerated approval under 21 CFR part 601, subpart E?

FDA response: With regards to the proposed plan to support a BLA under 21 CFR part 601, subpart E, there is insufficient information for FDA to determine:

- a) how the retrospective reclassification of PDL-1 positivity will affect the size of the study population in whom efficacy is being evaluated; and
- b) the adequacy of the results of BIRCH in providing an accurate estimate of the treatment effect

With regards to the proposed plan to support a PMA, it may be acceptable that the device analytical validation at the IHC 3+ cut-off will be completed prior to the primary analysis of BIRCH and not prior to the start of the study. This analytical validation data should be submitted in the PMA submission. Genentech should use data from studies outside of the BIRCH study to change the diagnostic cut-off from ^(b)₍₄₎% to 10% prior to unblinding and analysis of the data from the BIRCH study. These comments apply to the OAK study also if the cut-off will be changed.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question # 3: Genentech is planning to amend the BIRCH protocol to allow enrollment to remain open until a minimum of 75 IHC 3, 3L+ patients are enrolled. This would lead to approximately 100% power to detect a 25% increase in ORR from 5% to 30% at the 5% two-sided significance level. Does the Agency agree that 75 IHC 3, 3L+ patients

could be acceptable for a BLA filing and accelerated approval under 21 CFR part 601, subpart E?

Discussion during the meeting: FDA stated that Genentech's proposal may be acceptable; however this will depend on the magnitude of the ORR and duration of responses observed in the 75 patients with IHC 3+ tumors receiving third-line (or greater) treatment.

4. The Phase II Study GO28753 (POPLAR) in second-line/third-line NSCLC patients stratified by PD-L1 tumor status using a PD-L1 IHC assay will be conducted to assess the treatment effect of MPDL3280A in second-line/third-line NSCLC and to evaluate the efficacy in the populations defined by PD-L1 IHC 0, IHC 1, IHC 2, and IHC 3. Data from POPLAR will be used to determine if the pre-specified analyses in the Phase III Study GO28915 (OAK) are appropriate or if they should be modified. Specifically, the analysis as defined in the OAK protocol and SAP may be modified as laid out in the OAK Modification Plan (see Appendix 18).

Does the Agency agree with the proposed SAP for OAK (see Appendix 16)?

FDA response: The proposed hierarchal testing plan appears acceptable for controlling the type-I error rate. However, FDA is concerned that the test sequence starts by testing for efficacy in a subgroup of patients and ends by testing in all patients. FDA reaffirms earlier comments conveyed to Genentech at the February 12, 2013, meeting; that positive results for the overall population might be driven by positive results in patients the IHC 2/3+ stratum. The interpretation of additional analysis will be considered in light of the treatment effect in subgroups that are IHC 0 to 1+ or in complimentary subgroups.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question #4: Genentech acknowledged FDA's response to Question #4.

Discussion during the meeting: No further discussion occurred.

5. For each population group, the treatment comparison of OS will be at the 0.05 level of significance (two sided). For each population group, Kaplan-Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan-Meier curve will be constructed to provide a visual description of each arm. Estimates of treatment effect will be expressed as hazard ratio estimates using a stratified Cox model and 95% CIs. An unstratified log-rank test and hazard ratio estimates derived from unstratified Cox models will also be presented. No interim analyses will be performed.

Does the Agency agree with the plans proposed by the Sponsor to alter the OAK SAP and protocol if supported by POPLAR data, as described in the OAK Modification Plan?

FDA response: Yes. Genentech's SAP modification plans appear acceptable provided that the changes made are entirely based on the external data and that Genentech remains blinded to the results of OAK.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question #5: In the Agency's response to Questions 2 and 5 it states that Genentech's proposals appear acceptable provided that the changes made are entirely based on the external data and that Genentech remains blinded to the results of BIRCH/OAK. Genentech would like to clarify the following points regarding the conduct of BIRCH and OAK:

Population Level Data Summary:

- Genentech will remain blinded to the results of BIRCH and OAK (i.e. the population level efficacy data summaries) until the primary analysis.

Individual Patient Level Data:

- Genentech will remain blinded to patient PD-L1 IHC status for the BIRCH or OAK studies. Genentech will also remain blinded to treatment randomization assignment in the OAK study, with the only exception being patients who have serious adverse events as outlined in Genentech's internal SOPs.
- There will be a limited number of individuals on the study team at Genentech who will have access to patient level data, exclusive of patient PD-L1 IHC status (BIRCH and OAK) and treatment randomization assignment (OAK), e.g. data management and site monitors. However, these individuals with access to patient level data will be prohibited from conducting population level data summaries. Communication of clinical data between these individuals and others within Genentech will be strictly controlled and tracked.
- Separate Genentech teams that are independent of the study teams for BIRCH and OAK will only have access to the individual efficacy data in order to issue queries for data cleaning purposes. Efficacy data includes all tumor assessments and survival related data (i.e. treatment and study discontinuation and survival follow up data). Please Note: these individuals will not produce population level efficacy data summaries and will not have input on any modification to the BIRCH or OAK study. For OAK, this team will not have access to the treatment administration and randomization code. Communication between this separate team and others will be strictly controlled and tracked.

Discussion during the meeting: FDA acknowledged Genentech's clarifications. Genentech stated that their staff will not have access to the IHC status for individual patients or the randomization code. FDA agreed that the blinding procedures were acceptable. Based on clarifications from Genentech, and timelines provided on the attached slides, there will be adequate time for FDA review between receipt of cleaned external data from POPLAR and the proposed modification of the OAK trial. Genentech inquired whether the modifications would need FDA review prior to implementation.

FDA stated that Genentech should not wait for completion of FDA review of the data and should incorporate modifications and submit a revised SAP and protocol as a formal submission to the IND.

6. The current treatment paradigm for Study GO28915 (OAK) and Study GO28754 (BIRCH) has patients receiving treatment of MPDL3280A for up to 16 cycles or 1 year (whichever is sooner). Patients will then discontinue treatment with the possibility of re-treatment if disease progression occurs within 2 years after initial MPDL3280A discontinuation. This treatment paradigm is currently under evaluation in the ongoing Phase I Study PCD4989g, as well as in the Phase II Studies GO28625 (FIR) and GO28753 (POPLAR). Based on results from these studies, the Sponsor may amend the treatment duration in ongoing and future MPDL3280A studies to potentially extend the duration of treatment for some or all patients (e.g., a) initial treatment period of 16 cycles or 1 year in patients with a complete or partial response but treatment for up to 32 cycles or up to 2 years for patients with stable disease, or b) initial treatment to complete response or 2 years, whichever comes first, or c) initial treatment to 16 cycles or 1 year or best response plus 2 cycles, whichever comes later).

Does the Agency agree that the MPDL3280A treatment paradigm for OAK and BIRCH may be amended based on results from POPLAR and other ongoing MPDL3280A NSCLC studies up until the first time a patient in OAK and BIRCH, respectively, has completed the entire 16-cycle initial treatment stage of the study?

FDA response: Yes, FDA agrees with Genentech's proposal to modify the recommended dosing strategy of OAK and BIRCH before the first time a patient has completed 12 months or 16-cycles of treatment, whichever occurs first, based on evidence from POPLAR and other studies. However, please note that, in most circumstances, the dosage and administration in the product labeling would only reflect the dosing strategies used in the proposed studies.

FDA recommends that Genentech consider exploring strategies that compare shorter durations of treatment (e.g., 6 months of MPDL3280A in patients who attain a CR or PR) with more extended treatment durations.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question #6: Genentech acknowledged FDA's response to Question #6.

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

7. Does the Agency agree that the design of Study GO28915 (OAK) is adequate to support full approval of MPDL3280A for either of the following indications (in either a PD-L1-positive population or unselected population)?
- 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.

- MPDL3280A is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of a platinum-containing chemotherapy regimen.

FDA response: Demonstration of a highly statistically significant increase in OS that is sufficient to constitute direct clinical benefit in the proposed Study GO28915 (OAK) may be adequate to support a claim for MPDL3280A in patients previously treated with a platinum-containing chemotherapy regimen. The exact indication will be determined upon review of the application.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Question #7: Genentech acknowledged FDA's response to Question #7.

Discussion during the meeting: No further discussion occurred.

ADDITIONAL COMMENT:

Clinical

8. In the proposed protocols included in the meeting package, limit enrollment only to Stage IV NSCLC patients as defined by the American Joint Committee on Cancer (AJCC) Staging Manual, 7th Edition. Patients with stage IIIB disease should be enrolled if they are not candidates for multi-modality treatment.

Genentech's October 21, 2013, response to FDA's October 18, 2013, response to Comment # 8: Genentech believes that the current inclusion criteria in BIRCH and OAK which allows for patients with Stage IV, Stage IIIB (not eligible for definitive chemoradiotherapy), or recurrent NSCLC are consistent with FDA's request to limit enrollment to patients with Stage IV or Stage IIIB (not candidates for multi-modality treatment) NSCLC. Please refer to PMP Vol. 1 page 188-190 Protocol GO28754 (BIRCH) inclusion criteria and Vol. 2 page 49-50 Protocol GO28915 (OAK) inclusion criteria.

Discussion during the meeting: FDA stated that Genentech's proposed eligibility criteria are acceptable and acknowledged Genentech's commitment to ensure consistent eligibility for Stage IIIB (not eligible for definitive chemo-radiotherapy) patients across the FIR and BIRCH trials.

9. Consider conducting exploratory analyses of ORR, DOR, and PFS as measured by volumetric CT versus standard RECIST v1.1 assessments.

Discussion during the meeting: Genentech will make an effort to capture electronic radiographic CT data for exploratory analysis. FDA acknowledged Genentech's comment.