

On February 12, 2013, a meeting was held to discuss the clinical data from the Study PDC4989g and Genentech's proposed clinical development plan for MPDL3280A in for the treatment of patients with PD-L1-selected, locally advanced or metastatic, NSCLC that had progressed during or after platinum-based chemotherapy. FDA stated that to support a request for accelerated approval (AA) based on demonstration of a clinically meaningful response rate with adequate duration determined by independent review based on RECIST version 1.1, Study GO28754 (BIRCH) must demonstrate meaningful therapeutic benefit in this population over existing treatments (e.g., ability to treat patients unresponsive to or intolerant of, available therapy, or improved patient response over available therapy). FDA further stated that a coordinated review with CDRH is warranted to support accelerated approval of both MPDL3280A and the PD-L1 companion diagnostic and that patient selection and enrollment into the trials that support accelerated approval of both MPDL3280A and the PD-L1 companion diagnostic, should not begin until Genentech has provided demonstration of analytical robustness at the clinical decision point (cut-off) with a pre-specified testing protocol to the agency.

On March 26, 2013, Genentech submitted IND 117296 for the clinical development program for MPDL3280A for the treatment of NSCLC. The development program under this IND includes four ongoing studies enrolling patients receiving second (or greater) lines of therapy for NSCLC and six studies enrolling patients receiving first-line treatment for NSCLC.

On October 22, 2013, a meeting was held to discuss the acceptability of the protocols and Statistical Analysis Plans (SAPs) for BIRCH and Study GO28915 (OAK) in order to support accelerated and regular approval, respectively for MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC. FDA stated that the proposed modifications to the protocols and analysis plans for BIRCH and OAK appeared acceptable provided that the changes made were entirely based on external data and that the Genentech remain blinded to the results of BIRCH and OAK.

On December 5, 2014, Genentech submitted a request for Breakthrough Therapy designation (BTD) request for MPDL3280A for the development program in NSCLC. The BTD request was granted on January 28, 2015, for the treatment of patients with PD-L1 positive non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy, if EGFR- or ALK-positive.

On February 27, 2015, Genentech submitted a meeting request to discuss the results of the three dose-finding and activity-estimating studies, POPLAR, FIR and PCD4989g, conducted as part of the clinical development program for MPDL3280A for the treatment of patients with PD-L1-positive, NSCLC and to obtain preliminary advice on the content and format of the Summary of Clinical Safety (SCS), the integrated Summary of Safety (ISS), the Summary of Clinical Efficacy (SCE), the Integrated Summary of Efficacy (ISE) and on the acceptability of the proposed criteria for determination of which patient narratives will be included in Clinical Study Reports (CSRs) in the planned BLA.

On April 3, 2015, Genentech submitted a formal meeting request to discuss and reach agreement on the content and format of the proposed BLA.

Chemistry, Manufacturing, and Controls

MPDL3280A is a human IgG1 monoclonal antibody (mAb) 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.

Genentech states that MPDL3280A is being administered at a fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) by an intravenous infusion every 3 weeks. Two drug processes were used during clinical development. Study PCD4989g, FIR, and POPLAR used clinical trial material generated from the "Phase 1" process, while Study BIRCH used clinical trial material generated from the "Phase 3" process. Each single-use vial contains 1200 mg of MPDL3280A formulated as a sterile liquid for injection..

Clinical Pharmacology

The proposed dosage regimen for approval is MPDL3280A 1200 mg by intravenous (IV) infusion every 3 weeks. Genentech states that the BLA will contain data demonstrating that a fixed dose of 1200 mg will provide exposure equivalent to 15 mg/kg. Genentech indicates that a sponsor-defined data format for the population PK, the exposure-response, and concentration-QT analyses from BIRCH, POPLAR, FIR and PCD4989g will be submitted in the BLA. In addition, a PK comparison, using data obtained in the BIRCH study with drug product made under the "Phase 1" and "Phase 3" manufacturing processes obtained will be provided in the proposed BLA.

Finally, the BLA will contain the primary data (patient level results) for anti-drug antibodies and a summary of immunogenicity results for each study will be provided in the BLA submission, including an evaluation of the relationship of the immunogenicity response with PK, safety, and efficacy when appropriate.

Clinical

For the proposed BLA submission, Genentech plans to submit the results of four trials. The BIRCH trial will provide the primary evidence of anti-tumor activity and safety, while the POPLAR, FIR and PCD4989g studies will provide supportive evidence of activity and safety.

BIRCH Trial Design

The BIRCH study, a multicenter, three-arm, parallel cohort trial of MPDL3280A conducted in patients with PD-L1-positive (IHC 2+ or 3+), locally advanced or metastatic non-small cell lung cancer (NSCLC). The primary objective for this study is to evaluate the anti-tumor activity (overall response rate) of MPDL3280A as assessed by an Independent Review Facility (IRF) according to RECIST v1.1: The three cohorts are based on extent of prior treatment and defined as follows:

- Cohort 1: Patients who are chemotherapy-naïve (first-line treatment)
- Cohort 2: Patients who have received one prior line of platinum-based chemotherapy (second-line treatment)
- Cohort 3: Patients who have received 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))

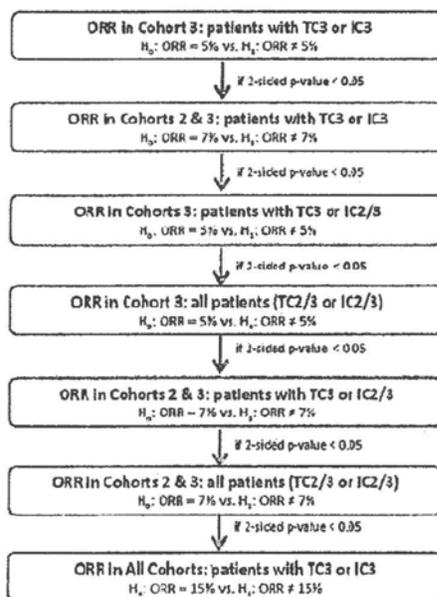
Patients with NSCLC containing ALK or EGFR mutations were eligible for enrollment in any of these three cohorts provided that they had exhibited disease progression during or following treatment with appropriate tyrosine kinase therapy.

Protocol-specified treatment in all cohorts is MPDL3280A 1200 mg intravenously every three weeks (Day 1 of each 21-day cycle). Patients in Cohort 1 are to receive MPDL3280A until RECIST-defined disease progression or unacceptable toxicity. Patients in Cohorts 2 and 3 are allowed 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.

Agreement on modifications to the final statistical analysis plan for the BIRCH study were reached during the December 9, 2014, meeting with FDA and the revised statistical analysis plan was submitted to IND 117296 on April 22, 2015. The primary efficacy analyses will successively test the IRF-assessed ORR per RECIST v1.1 in seven subpopulations; the overall type I error rate will be controlled at a two-sided α -level of 0.05, using a hierarchical fixed-sequence procedure. The hierarchical approach for analyses in these 7 subpopulations are outlined in Figure 1, below.

The primary analysis will be performed after approximately 100 patients with PD-L1 TC3 or IC3 NSCLC in Cohort 3 have a minimum of 6 months follow-up (or have discontinued). With approximately 100 patients who are PD-L1 TC3 or IC3 enrolled in Cohort 3, there is >99% power to detect a 25% increase in ORR from 5% to 30% in this population at the 5% two-sided significance level.

Figure 1. Hierarchical testing procedure in BIRCH



BIRCH Study – Results

Enrollment was completed in December 2014. The study enrolled a total of 667 patients across the three cohorts, as follows: 130 patients enrolled in Cohort 1, 255 patients enrolled in Cohort 2, and 282 patients enrolled in Cohort 3. Efficacy analyses have not been conducted.

Supportive studies

Further evidence for the efficacy and safety of MPDL3280A in the proposed BLA will be provided by supporting trials POPLAR, FIR and PCD4989g as outlined Table 1.

Table 1. Clinical trials evaluating the safety and efficacy of MPDL3280A in advanced NSCLC for the proposed BLA

Study	Design	Patient Population (No. of Patients Enrolled/Treated)	Treatment and Type of IHC Assay	Primary Efficacy Endpoint	Timing of Primary Analysis	Data Cutoff Date/Date of Data Availability
GO28754 (BIRCH)	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n=130) 2L (n=255) ≥3L (n=282)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥2L patients IUO IHC assay	IRF-assessed ORR per RECIST v1.1	Approximately 100 PD-L1 TC3 or IC3 patients in Cohort 3 with minimum 6 months follow-up	May 2015/ August 2015
GO28753 (POPLAR)	Open-label, randomized 1:1 to MPDL3280A vs. docetaxel	All comers with 1 or 2 prior chemotherapy regimens according to stratification: 1 prior chemotherapy (n=189) 2 prior chemotherapies (n=98)	MPDL3280A as a fixed dose of 1200 mg IV q3w until loss of clinical benefit; docetaxel 75mg/m ² IV q3w till disease progression or intolerable toxicity IUO IHC assay	Overall survival	A total of approximately 180 deaths have been observed in the overall population	May 2015/ July 2015
GO28625 (FIR)	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n=31) ≥2L (n=94) ≥2L with previously treated brain metastases (n=13)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥2L patients IUO IHC assay	Investigator-assessed ORR per modified RECIST v1.1	6 months after the last patient is enrolled	January 2015/ April 2015
PCD4989g	Multicenter, dose escalation, and expansion	PD-L1-selected and non-selected*; Enrollment completed for NSCLC cohort: 1L=15 2L=23 3L+=50	Weight-based dose escalation (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 15, and 20 mg/kg) and fixed 1200 mg dose, administered IV q3w up to 1 year or loss of clinical benefit Prototype IHC assay	Investigator-assessed ORR per RECIST v1.1 ^b	Data up to 2 December 2014	(NSCLC cohort only) December 2014/ April 2015

1L = first-line; 2L = second-line; 3L = third-line; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; IRF = Independent Review Facility; IUO = investigational use only; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

* FDA considers the OS analysis based on approximately 150 deaths as the final analysis.

^b The primary objective of this study is to evaluate the safety and tolerability of MPDL3280A. In order to further characterize the safety of MPDL3280A and to assess biomarkers of tumor activity in different cancer types, this study was amended to increase enrollment in the expansion cohort.

Proposed Clinical Contents of the BLA:

- Clinical Study Reports (CSRs) for the BIRCH, FIR, and PCD4989g trials
- An Integrated summary of safety (ISS) to include data from the BIRCH, POPLAR, FIR and PCD4989g trials in Module 5
- An Integrated summary of safety (ISE) to include data from the BIRCH, POPLAR, FIR and PCD4989g trials in Module 5
- Electronic Case Report Forms (eCRFs)
 - Deaths due to AEs (not related to disease progression)
 - Adverse events of special interest

- AEs leading to permanent study treatment discontinuation
- Adverse events which required treatment with systemic steroids.
- Annotated eCRFs will also be provided.
- Summaries of serious adverse events (SAEs) related to treatment, adverse events of special interest (both serious and non-serious), and all safety listings will include adverse events with onset date on or after the date of the first dose of study drug up to the data cutoff date of the corresponding individual studies.
- A listing of immune-mediated adverse events defined as any adverse events requiring the use of corticosteroids
- Safety summaries for treatment-emergent adverse events, other than adverse events of special interest (AESIs) or related SAEs, will include all adverse events that occur on or after the first dose of study drug and until the earliest of the following:
 - 30 days after the last administration of study drug
 - Initiation of another non-protocol anti-cancer therapy after the last administration of study drug
 - Clinical cutoff date

Genentech does not intend to include a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe and effective use of MPDL3280A for the proposed indication.

Genentech proposes to submit a 90-Day Safety Update in May 2016 based on updated information obtained in the BIRCH and POPLAR studies. The 90-Day Safety Update will include narratives for new cases and updated narratives for previously identified cases for patients who died due to AEs (excluding AE of disease progression), who had adverse events of special interest, who experienced AEs leading to treatment discontinuation, and who received systemic steroids for immune-mediated AEs.

Genentech states that the following ongoing trial is intended to verify the clinical benefit of for potential conversion to traditional approval:

- Study GO28915 (OAK) (last patient in [LPI] expected in June 2015, data maturity expected in Q3 2016), titled "Phase III, randomized, open-label study assessing the clinical benefit of MPDL3280A as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen."

OBJECTIVE

- The objective of this meeting is to obtain preliminary advice regarding the proposed content and format of the BLA.

QUESTIONS AND RESPONSES

General Comments

FDA reminds Genentech that the preliminary advice provided in preliminary meeting minutes regarding the content and format of the proposed BLA are intended as general advice to aid in decision-making. However this advice does not constitute formal agreements reached regarding the content of a complete BLA under the PDUFA V Program. Please ensure that a pre-BLA CMC only meeting is held prior to the interdisciplinary pre-BLA meeting at which agreements reached under the PDUFA V Program will be captured.

1. Does the Agency agree with the proposed plan for submitting the CSRs for the pivotal study BIRCH and supporting studies POPLAR, FIR and PCD4989g, as presented in Section 15.2?

FDA Response: Yes, FDA agrees with the proposal to submit the CSRs for the trials outlined in Table 4 of the meeting package to characterize the safety and efficacy of MPDL3280A.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

2. Does the Agency agree with the proposed submission of Electronic Case Report Forms (eCRFs) for the pivotal Study BIRCH, supporting studies POPLAR, FIR and PCD4989g (see Section 15.3.5)?

FDA Response: Yes, FDA agrees with the proposed submission of Electronic Case Report Forms (eCRFs) for the studies listed above. FDA may request additional CRF's during review of the marketing application.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

3. Does the Agency agree with the proposed content of the Module 5 datasets package submission, including the structure and format of the datasets for the pivotal Study BIRCH and supporting studies POPLAR, FIR and PCD4989g?

FDA Response: FDA agrees with the proposed format of the datasets for Studies BIRCH, POPLAR, FIR and PCD4989g.

The briefing package provides insufficient description of the dataset format for population PK, exposure-response, and concentration QT analyses. FDA recommends that Genentech clearly define "sponsor-defined" data format for these analyses in the pre-BLA briefing package and revisit this question as part of the pre-BLA meeting.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

4. Does the Agency agree with the plan not to provide radiographic images in the BLA, but to make these images available on request for the pivotal Study BIRCH?

FDA Response: Yes, FDA agrees with Genentech's plan not to provide radiographic images in the original BLA but to make them available upon request by FDA for BIRCH study.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

5. Does the Agency agree with the proposed reporting window for treatment-emergent adverse event (AE) summaries for the SCS and studies BIRCH, POPLAR, FIR, and PCD4989g?

FDA Response: At this time FDA does not agree with the proposed reporting window for adverse events in the SCS and Studies BIRCH, POPLAR, FIR, and PCD4989g. Provide additional justification based on evidence that adequate characterization of safety capturing a majority of immune-mediated treatment emergent adverse events will be detected in the proposed 30 day reporting window.

Genentech's June 26, 2015, electronic (email) response to question # 5: Genentech would like to clarify that AESI (sponsor-defined adverse event group terms of preferred terms representing immune-mediated reactions) and immune-mediated adverse events (adverse events requiring the use of systemic corticosteroids) will be analyzed without a defined reporting window.

Genentech would like to clarify the reporting window for the remainder of the adverse event summaries in the SCS (Section 15.5.1 of the PMP) and Studies BIRCH, POPLAR, FIR, and PCD4989g is acceptable.

Discussion during the teleconference: FDA acknowledged Genentech's clarification that the BIRCH Study used a different reporting window for AESI and immune-mediated adverse events as described above. Due to the differences in observation the BIRCH Study and the other three studies, FDA requested, and Genentech agreed, to pool AESI and immune-mediate adverse events from the three studies which used the 90-day reporting window and present data from the BIRCH Study separately as the BIRCH Study may have under-estimated the risks of these events.

FDA agreed that the alternative reporting window for non-immune mediated AEs is acceptable. Genentech agreed to provide analyses to support the FDA's request for characterization of immune-mediated adverse events.

6. Does the Agency agree with Genentech's proposal to not include a Risk Evaluation and Mitigation Strategy (REMS) for the use of MPDL3280A in advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) in the BLA?

FDA Response: At this time, FDA has insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of MPDL3280A outweigh the risks, and if it is necessary, what the required REMS elements will be. The need for a REMS will be determined during the review of the application. This question will be re-visited at the pre-BLA meeting.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

7. On the basis of existing data, are the planned content and format of clinical pharmacology and biopharmaceutics data in support of the BLA acceptable to the Agency?

FDA Response: FDA agrees with the proposed plan to include the following in the BLA submission.

- a. A summary of the pharmacokinetic results for Studies PCD4989g, FIR, POPLAR and BIRCH in the individual study reports and in the Summary of Clinical Pharmacology as appropriate.
- b. A population pharmacokinetic report for MPDL3280A using the available and relevant data from Studies PCD4989g, FIR, POPLAR and BIRCH that characterizes the pharmacokinetic properties of MPDL3280A and identifies the covariates that explain the between-patient variability of pharmacokinetic parameters.
- c. A report for exposure-response analysis for efficacy and safety of MPDL3280A using relevant data from Studies PCD4989g, FIR, POPLAR and BIRCH. In addition, include an assessment of covariates on MPDL3280A exposure-response relationships for efficacy and safety.
- d. A separate QTc report for the effect of MPDL3280A on the QT/QTc interval and the concentration-QTc analysis using data from PCD4989g.
- e. A summary of immunogenicity results for each study (in the individual study report) and across studies (as a separate report or in Summary of Clinical Safety) that includes a characterization of the relationship of the immunogenicity response with MPDL3280A pharmacokinetics, safety, and efficacy where appropriate.
- f. A summary of the analytical and pharmacokinetic comparability of the "Process 1" and "Process 3" drug products administered to patients in the BIRCH trial should be provided in the Summary of Clinical Pharmacology and the individual study report.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

8. Does the Agency agree with Genentech's proposal for a 90 day Safety Update?

FDA Response: Yes, FDA generally agrees with Genentech's proposed content for the 90 day Safety Update.

Genentech's June 26, 2015, electronic (email) response to question # 8: Genentech acknowledges the Agency's feedback and would like to clarify the following content of the 90 day safety update:

Updated safety data analyses for individual studies BIRCH and POPLAR, no pooled analyses.

- All deaths
- SAE tables
- AEs leading to study drug discontinuation
- AE tables
- AESIs
- Per FDA request for initial BLA, the following will also be included in the 90 day safety update: data on AEs requiring the use of corticosteroids with no clear alternate etiology (including time to onset of event, time to start of corticosteroids/other immunosuppressive agents, dose of corticosteroids/other immunosuppressive agents, duration of corticosteroids/other immunosuppressive agents, AE outcome, and duration of event from onset until documented resolution)

Discussion during the teleconference: FDA requested, and Genentech agreed to provide, pooled analyses for the BIRCH and POPLAR Studies for AESI's and immune-mediated adverse events. FDA stated that otherwise the proposal is acceptable.

9. Does the Agency agree with Genentech's plans for the collection and organization of supporting documentation for the overall Table of Contents of the BLA?

FDA Response: The proposed approach in which Modules 3 and 4 will be submitted in the cross-referenced BLA for treatment of bladder cancer appears acceptable; however, this will be re-visited at the time of the pre-BLA meeting.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

10. Genentech acknowledges FDA's preliminary comments for the 12 May 2015 Type B meeting (received 11 May 2015) and the discussion during the meeting indicating that, for the POPLAR study, FDA considers the OS analysis, based on approximately 150 deaths, as the final OS analysis, but does not object to reviewing an exploratory analysis based on 180 deaths,

Does the Agency agree with Genentech's proposal to use and submit in the BLA the datasets associated with approximately 180 deaths in the POPLAR study?

Specifically:

- a. Efficacy analysis results associated with both approximately 150 deaths and approximately 180 deaths will be provided in the POPLAR CSR.

FDA Response: Yes, however, the analysis based on 180 deaths will be considered exploratory.

Genentech's June 26, 2015, electronic (email) response to 10 (a): Safety analysis results and narratives associated with approximately 180 deaths will be used in the POPLAR CSR.

Discussion during the teleconference: FDA stated that Genentech's proposal was acceptable.

- b. Safety analysis results and narratives associated with approximately 180 deaths will be used in the POPLAR CSR.

FDA Response: Yes, FDA agrees.

Discussion during the teleconference: Genentech acknowledges the Agency's feedback. No further discussion is needed.

- c. The proposed POPLAR datasets associated with approximately 180 deaths will be used in the SCE/ISE and SCS/ISS pooled analyses.

FDA Response: Yes, provided that integrated efficacy analyses are also presented based on 150 deaths in POPLAR.

Genentech's June 26, 2015, electronic (email) response to 10 (c): Genentech acknowledges the Agency's feedback and will provide the integrated efficacy analyses based on approximately 150 deaths and approximately 180 deaths in POPLAR.

Discussion during the teleconference: FDA stated the Genentech's proposal is acceptable.

- d. Only datasets associated with approximately 180 deaths will be submitted in the BLA. The datasets associated with approximately 150 deaths will not be provided separately.

FDA Response: This is acceptable only if the dataset associated with approximately 180 deaths contains an indicator that can identify the primary analysis population for POPLAR based on 150 deaths.

Genentech's June 26, 2015, electronic (email) response to 10 (d): Genentech acknowledges the Agency's feedback. Separate datasets associated with the analysis that has been conducted with approximately 150 deaths as well as datasets associated with approximately 180 deaths will be submitted in the BLA.

Discussion during the teleconference: FDA stated the Genentech's proposal is acceptable.

ADDITIONAL COMMENTS

11. For regulatory purposes, the primary analyses of ORR in the BIRCH study will be performed on all treated patients, i.e., all patients who received any dose of the study drug during the study treatment period, regardless of whether patients have measurable disease at baseline.

Genentech's June 26, 2015, electronic (email) response to additional comment # 11: Genentech acknowledges the Agency's feedback and will conduct the primary ORR analysis in BIRCH on all treated patients, i.e., all patients who received any dose of the study drug during the study treatment period, regardless of whether patients have measurable disease at baseline.

Genentech would also like to clarify the following four points:

- a. In reference to IND 117296 (Serial No. 0260), Genentech plans to exclude (b) (4) [REDACTED] in all efficacy analyses.

Discussion during the teleconference: FDA did not agree with Genentech's proposal. The BLA must contain data from all patients registered on the protocol and the primary efficacy analysis must include all patients registered on trial who received any part of any dose of study drug.

Genentech may also provide the results of efficacy analysis which exclude (b) (4) [REDACTED] with a justification as to why such data are not reliable. FDA will independently review and decide on the appropriate analysis population for labeling and promotion claims during review of the BLA.

Genentech acknowledged FDA's comments and agreed to present the data as requested by FDA.

- b. In PCD4989g, all treated lung patients have measurable disease at baseline. This study has already been analyzed and the CSR outputs will remain as is.

Discussion during the teleconference: Please see FDA response under 11(d).

- c. In FIR, 1 out of 137 treated patients did not have measurable disease at baseline. This study has already been analyzed and has excluded 1 patient without measurable disease in the ORR analysis. The CSR output will remain as is.

Discussion during the teleconference: Please see FDA response under 11(d).

- d. In addition to the BIRCH study ORR analysis, does the Agency intend for the SCE/ISE ORR analysis to be performed on all treated patients, i.e., all patients who received any dose of the study drug during the study treatment period, regardless of whether patients have measurable disease at baseline?

Discussion during the teleconference: FDA agreed that Genentech's proposal made during the meeting that the efficacy analysis of all studies individually and in the SCE/ISE will be conducted in all patients registered on trial who received any part of a dose of study drug.

Additional Discussion points between FDA and Genentech

- Genentech stated that a planned database lock, for the BIRCH Study, will be August 6, 2015. Data will be available for review August 13, 2015, and will be submitted to the IND.
- Genentech stated that the pre-BLA CMC only meeting for original BLA (seeking approval for treatment of urothelial bladder cancer) to be held under IND 120827, is scheduled for July 29, 2015. IND 120827 is managed by the Division of Oncology Products 1. This is acceptable; any agreements reached during this meeting will be applicable to a BLA for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is PD-L1 selected, as determined by an FDA-approved test, after failure of a platinum-containing chemotherapy regimen, in the event that the planned BLA for the treatment of bladder cancer is delayed.
- Genentech stated that pre-BLA all discipline meeting for IND 117296 is planned for October 2015 with submission of the marketing application in February 2016.
- Ventana will initiate the premarket approval (PMA) with the Center for Devices and Radiologic Health (CDRH).

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.

FDA acknowledges receipt of Genentech's Agreed Initial Pediatric Study Plan (iPSP), submitted on February 6, 2015, and also refers to FDA's letter, dated May 8, 2015, confirming FDA's agreement with the iPSP. This fulfills Genentech's requirements under the IND at this stage of development to reach an Agreed iPSP with the Agency, as required by FDASIA for products that would trigger PREA at the time of BLA submission.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

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/ucm372553.htm>)

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/s/

GINA M DAVIS
07/08/2015



IND 117296

MEETING MINUTES

Genentech, Inc.
Attention: Nitzan Sternheim, PhD
Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Sternheim:

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 initial breakthrough designation meeting between representatives of your firm and the FDA on May 12, 2015. The purpose of the meeting was to discuss the results of supportive studies (POPLAR, FIR and PCD4989g) to be included in the proposed BLA seeking accelerated approval for MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1 selected with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy, if EGFR or ALK positive.

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

Enclosures:
Meeting Minutes
Office of Scientific Investigations – Bioresearch Monitoring Clinical Data in eCTD Format
Attendance Sheet



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Initial Advisory Meeting Breakthrough Designated Product
Meeting Date and Time: May 12, 2015 – 12:00 PM – 1:00 PM
Meeting Location: CDER WO 22 – Conference Room 1421
Application Number: 11-7296
Product Name: MPDL3280A
Indication: non-small cell lung cancer (NSCLC)
Sponsor/Applicant Name: Genentech, Inc.

FDA ATTENDEES

Center for Drugs Evaluation and Research

Office of Hematology and Oncology Products

Division of Oncology Products 1 (DOP 1)
Virginia Maher, M.D. Medical Team Lead, DOP 1

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

Office of Biostatistics

Division of Biostatistics V (DB V)
Janet Jiang, Ph.D., Biostatistics Reviewer, DB V

Office of Clinical Pharmacology

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

Office of Scientific Investigations

Division of Clinical Compliance Evaluation (DCCE)
Lauren Iacono-Connors, PhD., Clinical Inspector, DCCE

Center for Devices and Radiologic Health

Office of In Vitro Radiology

Molecular Pathology and Cytology Branch (MPCB)

Prakash Jha, MD, MPH, Medical Officer, MPCB

Shyam Kalavar, MPH, CT (ASCP), Scientific Reviewer, MPCB

Division of Medical Genetics and Pathology (DMGP)

Reena Philip, PhD., Director, DMGP

SPONSOR ATTENDEES

Genentech

Cathi Ahearn, M.B.A., Lifecycle Team Leader, Global Product Strategy Oncology

Dietmar Berger, M.D., Ph.D., Senior Vice-President, Clinical Hematology/Oncology

Nicholas Bruno, Global Regulatory Leader, Product Development Regulatory

Daniel Chen, M.D., Ph.D., Senior Group Director, Product Development Clinical Oncology

Andrew Chia, Pharm.D., M.S., Regulatory Program Management, Product Development
Regulatory

David Chonzi, M.D., MPFPM, M.Sc., Safety Science Leader, Pharma Development Safety Risk
Management

Karen Jones, Vice-President and Global Head Oncology, Product Development Regulatory

Marcin Kowanetz, Ph.D., Scientist, Oncology Biomarker Development and Diagnostics

Zhengrong Li, Ph.D., Senior Statistical Scientist, Biostatistics

Simonetta Mocci, M.D., Ph.D., Medical Director, Product Development Clinical Oncology

Alan Sandler, M.D., Principal Medical Director, Product Development Clinical Oncology

Priti Hegde, Ph.D., Senior Scientist, Oncology Biomarker Development

Dustin Smith, Ph.D., Companion Diagnostics Manager, Oncology Biomarker Development

Nitzan Sternheim, Ph.D., Regulatory Program Management, Product Development Regulatory

Jing Yi, Ph.D., Principal Statistical Scientist, Biostatistics

Ventana

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

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 12, 2015, from 12:00 PM – 1:00 PM between Genentech, Inc., and the DOP 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine

that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Regulatory History

On 11 April 2011, Genentech submitted an IND (IND 111271) for MPDL3280A for the treatment of locally advanced and metastatic malignancies. The IND-enabling trial was Protocol PCD4989g entitled "A Phase I, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of MPDL3280A Administered Intravenously as a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors or Hematologic Malignancies."

On 12 February 2015, a meeting was held to discuss the clinical data from the Study PDC4989g and their proposed clinical development plan for MPDL3280A in for the treatment of patients with PD-L1–selected locally advanced or metastatic NSCLC that had progressed during or after standard platinum-based chemotherapy. FDA stated that for the clinical program to be considered for accelerated approval (AA) based on durable objective responses, Study GO28754 (BIRCH) would need to include patients with unmet medical need with NSCLC.

On 26 March 2013, Genentech submitted IND 117296 for the investigational product MPDL3280A for the treatment of NSCLC with four ongoing studies enrolling 2L + NSCLC patients and six planned ongoing studies enrolling 1L NSCLC patients.

On 22 September 2013, Genentech submitted a preliminary breakthrough therapy designation (BTD) for MPDL3280A in (b)(4) NSCLC in patients on the basis of interim data from the POPLAR study.

On 22 October 2013, a meeting was held to discuss the acceptability of the protocols and Statistical Analysis Plans (SAPs) for BIRCH and Study GO28915 (OAK) in order to support accelerated and regular approval, respectively for MPDL3280A for the treatment of patients with locally advanced or metastatic NSCLC. FDA stated that the proposed modifications to the protocols and analysis plans for BIRCH and OAK appeared acceptable provided that the changes made were entirely based on external data and that the Genentech remain blinded to the results of BIRCH and OAK.

On 5 December 2014, Genentech submitted a formal request for BTD for MPDL3280A, which was granted BTD on 28 January 2015 for the treatment of patients with locally advanced or metastatic NSCLC that is PD-L1 selected with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

On 9 December 2014, a meeting was held to seek FDA guidance regarding the proposed changes to the definition of PD-L1 positivity in NSCLC and resulting modified hypothesis testing procedures for the ongoing clinical studies, OAK and BIRCH. The FDA agreed that demonstration of an ORR of large magnitude and duration in [REDACTED] (b) (4) [REDACTED] BIRCH with a favorable benefit-risk profile could potentially support accelerated approval of MPDL3280A in previously treated NSCLC with disease progression on or after platinum-based chemotherapy and appropriate targeted therapy if EGFR or ALK positive.

On 27 February 2015, Genentech submitted a meeting request to discuss the results of the three dose-finding and activity-estimated studies, POPLAR, FIR and PCD4989g under their development program for MPDL3280A for treatment of PD-L1-positive, NSCLC and to obtain preliminary advice on the content and format of the Summary of Clinical Safety (SCS), the integrated Summary of Safety (ISS), the Summary of Clinical Efficacy (SCE) and the Integrated Summary of Efficacy (ISE) as well as advice on the acceptability of the proposed categories of patient narratives to be included in Clinical Study Reports (CSRs) in the planned BLA.

Chemistry, Manufacturing and Controls

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.

Genentech states that MPDL3280A is administered at a fixed dose of 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) by an intravenous (IV) infusion every 3 weeks. MPDL3280A is expressed in suspension cultures of CHO cells. Each single-use vial contains 1200 mg [REDACTED] (b) (4) of MPDL3280A as a sterile liquid (Phase III process). Studies PCD4989g, FIR, and POPLAR are being conducted using clinical trial material generated from the Phase I process, while BIRCH is being conducted using clinical trial material generated from the Phase III process. The Investigator Brochure suggests that there were no meaningful differences in exposure following administration of drug product produced using these different manufacturing processes.

Toxicology

The toxicology program was designed to support IV or subcutaneous (SC) administration of MPDL3280A to patients for up to 2 months in initial clinical trials. The program consisted of a 15-day pilot study in mice with a 4-week recovery period, an 8-week repeat-dose study in cynomolgus monkeys with a 12-week recovery period, an in vitro cytokine release assay, an in vitro hemolytic potential evaluation, and a tissue cross-reactivity analysis of human and cynomolgus monkey tissues.

. In addition, Genentech has provided a revised literature-based justification for not conducting reproductive and developmental toxicology studies with MPDL3280A.

Clinical/Statistical

The trials intended to support the proposed BLA (planned submission February 2016) in previously treated advanced NSCLC are summarized below (Table-1). Genentech proposes to support an initial request for accelerated approval based on the results of the Study GO28754 (BIRCH), in which the last patient was enrolled in December 2014 and the data cut-off data is anticipated to be June 2015: The BIRCH trial is a single-arm study assessing the overall response rate and durability of response with MPDL3280A in patients with PD-L1 positive, locally advanced or metastatic NSCLC patients receiving first-, second-, or third-line or greater therapy. The proposed BLA will also be supported by the results of Studies GO28625 (FIR) and PCD4989g, which will provide information on ORR and duration of response with MPDL3280A in patients with PD-L1 positive (FIR) or unselected for PD-L1 (PCD4989g), locally advanced or metastatic NSCLC patients receiving first-, second-, or third-line or greater therapy. In addition, the planned BLA will be supported by the results of Study GO28753 (POPLAR), which will provide an estimate of the overall survival effect of MPDL3280A compared to docetaxel in the second-line treatment of patients with NSCLC. In the POPLAR trial, randomization was stratified by PD-L1 immune cell status.

Table 1 – Clinical Studies to be included in efficacy and safety summaries evaluating MPDL3280A in Proposed BLA

Study	Design	Patient Population (No. of Patients Enrolled/Treated)	Treatment and Type of IHC Assay	Primary Efficacy Endpoint	Timing of Primary Analysis
GO28754 (BIRCH) Efficacy	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n = 130) 2L (n = 255) ≥ 3L (n = 282)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥ 2L patients IUO IHC assay	IRF-assessed ORR per RECIST v1.1	Approximately 100 PD-L1 TC3 or IC3 patients in Cohort 3 with minimum 6 months follow-up
GO28753 (POPLAR) Supportive	Open-label, randomized 1:1 to MPDL3280A vs. docetaxel	All comers with 1 or 2 prior chemotherapy regimens according to stratification: 1 prior chemotherapy (n = 189) 2 prior chemotherapies (n = 98)	MPDL3280A as a fixed dose of 1200 mg IV q3w until loss of clinical benefit; docetaxel 75mg/m ² IV q3w till disease progression or intolerable toxicity IUO IHC assay	Overall survival	A total of approximately 180 deaths have been observed in the overall population
GO28625 (FIR) Supportive	Multicenter, single arm	PD-L1 TC2/3 or IC2/3 : 1L (n = 31) ≥ 2L (n = 94) ≥ 2L with previously treated brain metastases (n = 13)	MPDL3280A as a fixed dose of 1200 mg IV q3w until disease progression for 1L patients and loss of clinical benefit for ≥ 2L patients IUO IHC assay	Investigator-assessed ORR per modified RECIST	6 months after the last patient is enrolled
PCD4989g Supportive	Multicenter, dose escalation, and expansion	All comers, enrollment ongoing a; for NSCLC cohort 1L = 15 2L = 23 3L + = 50	Weight-based dose escalation (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 15, and 20 mg/kg) and fixed 1200 mg dose, administered IV q3w up to 1 year or loss of clinical benefit Prototype IHC assay	investigator-assessed ORR per RECIST v1.1 a	Data up to 2 December 2014

1L = first-line; 2L = second-line; 3L = third-line; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; IRF = Independent Review Facility; IUO = investigational use only; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; q3w = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell. The primary objective of this study is to evaluate the safety and tolerability of MPDL3280A. In order to further characterize the safety of MPDL3280A and to assess biomarkers of tumor activity in different cancer types, this study was amended to increase enrollment in the expansion cohort.

An IHC scoring criteria has been formulated to characterize the intensity of PD-L1 expression in tumor cells (TC) and in tumor-infiltrating immune cells (IC) for the purpose of defining level of PD-L1-positivity for retrospective analyses and labeling claims (Table 2).

Table 2. Proposed Criteria for PD-L1 Expression Assessment in Planned BLA

Description of IHC Scoring Algorithm	PD-L1 Expression Level
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering <1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between $\geq 1\%$ and <5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between $\geq 5\%$ and <10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering $\geq 10\%$ of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in <1% TCs	TC0
Presence of discernible PD-L1 staining of any intensity in $\geq 1\%$ and <5% TCs	TC1
Presence of discernible PD-L1 staining of any intensity in $\geq 5\%$ and <50% TCs	TC2
Presence of discernible PD-L1 staining of any intensity in $\geq 50\%$ TCs	TC3

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death-ligand 1; TC = tumor cell.

Since none of the patients in the clinical development program were identified as having PD-L1-positive NSCLC based on the validated TC3 and IC3 cutoffs as outlined in Table 2, tumor samples from these trials will be rescored to the validated TC3 to IC3 cutoff using a stepwise algorithm prior to database lock (Table 3). Samples from POPLAR will also be rescored to the TC2 to IC2 cutoff using the stepwise algorithm prior to database lock. For BIRCH, Genentech proposes to use the TC2 and IC2 cutoff enrollment data. The final analysis of POPLAR and BIRCH will be based on the PD-L1 IHC status defined by a cutoff using the stepwise algorithm.

Table 3. Stepwise PD-L1 TC2 to IC2 Scoring Algorithm

Step 1: Tumor Cell (TC) Staining Assessment	PD-L1 Score	PD-L1 Status
Absence of any discernible VENTANA PD-L1 (SP142) assay staining OR Presence of discernible membrane VENTANA PD-L1 (SP142) assay staining of any intensity in <5% of tumor cells	TC0/1	Negative (Move to Step 2)
Presence of discernible membrane VENTANA PD-L1 (SP142) assay staining of any intensity in ≥5% of tumor cells	TC2/3	Positive (Do not move to Step 2)
Step 2 (only if negative in Tumor-Infiltrating Immune Cell (IC) Step 1): Staining Assessment	PD-L1 Score	PD-L1 Status
Absence of any discernible VENTANA PD-L1 (SP142) assay staining OR Presence of discernible VENTANA PD-L1 (SP142) assay staining of any intensity in tumor-infiltrating immune cells covering <5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0/1	Negative
Presence of discernible VENTANA PD-L1 (SP142) assay staining of any intensity in tumor-infiltrating immune cells covering ≥5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2/3	Positive

Results of supportive studies for planned BLA

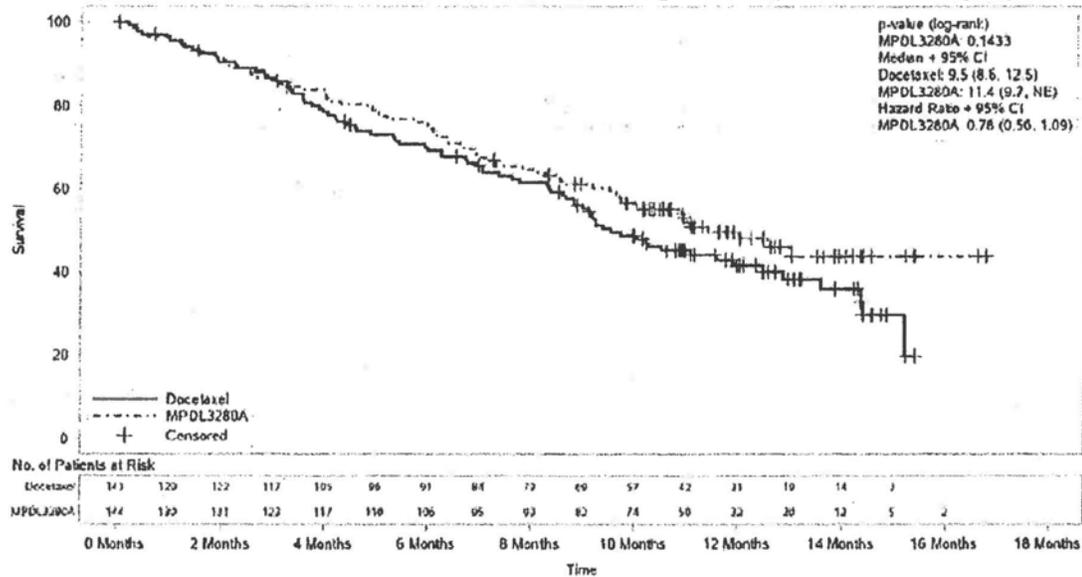
POPLAR Study

The primary efficacy endpoint (OS) in POPLAR and the secondary objectives (PFS, ORR, DOR) were assessed in the ITT population. In the meeting package, Genentech included an updated statistical analysis plan (SAP) for POPLAR trial, for the conduct of these exploratory subgroup analyses based on emerging data from FIR and Study PCD4989g. Evaluation of efficacy endpoints in PD-L1–selected subgroups will be conducted in a stepwise manner, as listed below:

- TC3 or IC3 and complementary group TC 0/1/2 and IC0/1/2
- TC3 or IC2/3 and complementary group TC0/1/2 and IC0/1
- TC2/3 or IC2/3 and complementary group TC0/1 and IC0/1
- TC1/2/3 or IC1/2/3 and complementary group TC0 and IC0

Genentech presents the results of POPLAR based on a January 30 2015 data-cut as an interim analysis of overall survival conducted in the 287 patients in the ITT population (144 and 143 patients in the MPDL3280A and docetaxel treatment arms, respectively). A trend towards OS benefit in the MPDL3280A arm was observed, with a stratified HR of 0.78 (95% CI: 0.59, 1.03) (Figure 1).

Figure 1. Overall Survival in POPLAR: ITT Population (Stratified Analysis)



These result of the PD-L1 subgroup analyses are presented in Table 4

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Table 4. POPLAR Efficacy Results in Various PD-L1 Subgroups Using the “Rescored” Cut-Offs

Diagnostic Subgroup	OS HR (95% CI)	PFS HR (95% CI)	ORR (MPDL/Doc)	Total No. of Patients (MPDL/Doc)
TC3 or IC3	0.47 (0.20, 1.11)	0.56 (0.28, 1.11)	37.5%/13.0%	47 (24/23)
TC0/1/2 and IC0/1/2	0.88 (0.62, 1.24)	1.08 (0.81, 1.44)	10%/15.8%	240 (120/120)
TC3 or IC2/3	0.52 (0.28, 0.95)	0.64 (0.38, 1.08)	25%/16.2%	77 (40/37)
TC0/1/2 and IC0/1	0.93 (0.64, 1.36)	1.14 (0.84, 1.55)	10.6%/15.1%	210 (104/106)
TC2/3 or IC2/3	0.56 (0.33, 0.95)	0.70 (0.45, 1.08)	22.0%/14.5%	105 (50/55)
TC0/1 and IC0/1	0.98 (0.65, 1.49)	1.16 (0.84, 1.62)	10.6%/15.9%	182 (94/88)
TC1/2/3 or IC1/2/3	0.63 (0.42, 0.95)	0.87 (0.63, 1.20)	18.3%/17.6%	195 (93/102)
TC0 and IC0	1.22 (0.69, 2.14)	1.15 (0.72, 1.82)	7.8%/9.8%	92 (51/41)

HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Notes: The HRs for OS and PFS are un-stratified values. The ORRs are for confirmed responses.

Additional subgroup analyses were conducted by tumor histology and are presented in the table below. Similar ORRs (about 15%) were observed in both subgroups with MPDL3280A.

Table 5. POPLAR Efficacy Results by Histologic Subtype

Endpoint	Squamous NSCLC	Non-squamous NSCLC
Overall survival	HR 0.88 [95% CI: 0.53, 1.47]	HR 0.76 [95% CI: 0.5, 1.14]
Progression-free survival	HR 0.72 [95% CI: 0.46, 1.12]	HR 1.06 [95% CI: 0.76, 1.47]

Study PCD4989g

The meeting package contained results from Study PCD4989g using a September 2, 2014 data cutoff. These analyses are based on 88 patients with NSCLC identified as “evaluable” for efficacy. There were 18 patients identified with an objective response for an ORR per RECIST v1.1 (confirmed) of 20.5% (95% CI: 12.6%, 30.4); the median duration of response is 15.4 months (95% CI: 14.2, 24.7). There were 20 patients retrospectively identified as having PD-L1 positive disease (TC3 or IC3); the ORR in the PD-L1 positive subgroup is 45% (9/20), with a median duration of response of 14.6 months (95% CI: 7.5, NE).

Study FIR

The meeting package provides the results for ORR in 71 “efficacy-evaluable” patients receiving second- or greater line of therapy ($\geq 2L$). In these patients, the ORR is 17% (95% CI: 8.18, 25.62) and the median duration of response has not yet been reached according to Genentech. Among patients retrospectively identified as having PD-L1 positive disease (TC3 or IC3); the ORR in the PD-L1 positive subgroup is 27% (Table 5).

Table 6. Efficacy Results in Study PCD4989g and FIR: Efficacy-Evaluable Patients and PD L1 Subgroups

Efficacy Endpoint	Study PCD4989g ^a			FIR ^b		
	Efficacy Evaluable (n=88)	TC3 or IC3 (n=20)	TC3 or IC2/3 (n=37)	Efficacy Evaluable (i.e., TC2/3 or IC2/3) (n=71)	TC3 or IC3 (n=26)	TC3 or IC2/3 (n=63)
ORR	21% (18 of 88)	45% (9 of 20)	32% (12 of 37)	17% (12 of 71)	27% (7 of 26)	18% (11 of 63)
Median duration of response (mths) (95% CI)	15.4 (14.2, 24.7)	14.6 (7.5, NE)	14.6 (8.7, 25.3)	NE (10.4, NE)	NE (10.4, NE)	NE (10.4, NE)
Median PFS (mths) (95% CI)	2.8 (1.9, 8.5)	3.3 (1.4, 11.5)	2.8 (1.41, 11.1)	2.7 (1.4, 3.1)	3.1 (1.6, 15.3)	2.7 (1.4, 4.5)
24-week PFS (%) (95% CI)	42.40 (31.84, 52.96)	45 (23.20, 66.80)	41.67 (25.56, 57.77)	34.91 (23.46, 46.36)	49.23 (29.76, 68.70)	34.49 (22.31, 46.67)
1 year OS (%) (95% CI)	81.67 (72.36, 90.99)	89.06 (74.67, 100)	81.29 (67.62, 94.97)	NA	NA	NA

NA=not applicable; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

^a Data for the PD-L1 subgroup of TC2/3 or IC2/3 are currently not available for Study PCD4989g.

^b Only Cohort 2 patients.

Timelines for Genentech's proposed BLA are shown below:

Key Data and Submission Milestones/Agency Meetings	Estimated Date
Database lock Study PCD4989g 1L+NSCLC cohort (supportive)	March 2015
CDRH information meeting ^a	March 2015
CDRH Pre-Submission meeting ^a	Q2 2015
Database lock FIR (Study GO28625) 1L/2L+ (supportive)	April 2015
Type B Multidisciplinary meeting ^b	12 May 2015
Type B Content and Format Meeting	June 2015
Database lock POPLAR (Study GO28753) 2L/3L (supportive)	July 2015
Database lock BIRCH (Study GO28754) 1L/2L+ (pivotal)	August 2015
CMC Pre-BLA Type B meeting	August 2015
CMC and nonclinical Modules 3 and 4 and related summaries submission ^c	October 2015
Type B Pre-BLA meeting	October 2015
Module 2 summaries and Module 5 submission ^d	February 2016

2L=second line; 3L=third line; BLA=Biologics License Application; IHC=immunohistochemistry; UBC=urothelial bladder cancer.

^a Meeting covers both NSCLC and UBC programs.

^b The Type B Multidisciplinary meeting after the Breakthrough Therapy Designation was granted to MPDL3280A in UBC was held on 8 October 2014.

^c Assumes as rolling submission. These modules would be submitted first as part of the UBC BLA. For the lung BLA, Sponsor proposes to cross reference the contents in the UBC BLA.

^d Modules 2 and 5 for the UBC BLA are proposed to be submitted in January 2016.

OBJECTIVES

- To provide and discuss the updated data from POPLAR, FIR, and Study PCD4989g
- To reaffirm with the Agency that data from the Study GO28754(BIRCH), as supported by the results of the POPLAR, FIR, and Study PCD4989g studies, would be able to support the filing of an application for accelerated approval (AA) in for the treatment of patients with previously treated NSCLC

- To gain agreement as to the requirements that will enable the inclusion of additional PD-L1–selected populations in the label that may be supported by clinical data from BIRCH and POPLAR
- To gain agreement on the revised Statistical Analysis Plans (SAPs) for POPLAR, the SCS and ISS, and the SCE and ISE; on the content and format of the SCS and ISS and the SCE and ISE; and on the categories of patient narratives to be provided

DISCUSSION

General Comments:

As noted in FDA’s January 28, 2015, letter informing Genentech that Breakthrough Therapy Designation for MPDL3280A was granted for the proposed designation, FDA advised Genentech to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy, as described in the MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy- Designated Drugs and Biologics.

FDA notes that this meeting does not request discussion of the development program with regard to Chemistry, Manufacturing, and Controls, Non-Clinical Pharmacology and Toxicology, nor Clinical Pharmacology data. In addition, it is unclear whether Genentech has responded to all outstanding issues with regard to the validation of the proposed companion diagnostic device for identification of PD-L1-positive NSCLC. Genentech is strongly encouraged to review their development program and ensure that requirements for submission of a complete application can be met for MPDL3280A and of the companion diagnostic program for the associated device, in the context of this development program.

In addition, FDA reminds Genentech that the preliminary advice provided in FDA responses regarding content and format of the proposed BLA are intended as general advice to aid in decision-making. However this advice does not constitute formal agreements reached regarding the content of a complete BLA under the PDUFA V Program. Please ensure that a pre-BLA CMC only meeting is held prior to the interdisciplinary pre-BLA meeting at which agreements reached under the PDUFA V Program will be captured.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Given the changing landscape in metastatic squamous NSCLC (b) (4), does the Agency agree that data from BIRCH and supportive data from POPLAR, FIR, and Study PCD4989g in a PD-L1–selected patient population, TC3 or IC3, remain eligible for AA in previously treated NSCLC per 21 CFR part 601, subpart E?

FDA Response: FDA acknowledges the previous statements in the December 9, 2014, meeting minutes, that demonstration of ORR of large magnitude and duration in BIRCH, which is consistent with Genentech's hierarchical testing procedure presented at the meeting and which 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" with a favorable benefit-risk profile, can potentially support accelerated approval of MPDL3280A under 21 CFR Part 601, subpart E for the treatment of patients with an unmet medical need, i.e., previously treated metastatic NSCLC for whom there is no satisfactory alternative therapy. These statements were made in the context of available therapy for NSCLC which has changed and now includes nivolumab for the second-line treatment of patients with squamous cell NSCLC. Therefore, in any application seeking accelerated approval, Genentech must provide evidence that the treatment effect observed provides a substantial improvement over available therapy or that the population has no alternative therapy. Evidence of a substantial improvement over available therapy may be demonstrated if the lower bound of the 95% CI around the observed effect in Cohort 3, TC3/IC3 subgroup exceeds the upper bound of the 95% CI of observed with nivolumab.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 1: Genentech acknowledges that a path for accelerated approval exists for products that demonstrate a substantial improvement over available therapy in patients with an unmet medical need. Genentech would like to clarify the relevant nivolumab response rate benchmark for NSCLC.

Discussion during the meeting: FDA clarified that evidence of a substantial improvement over available therapy may be demonstrated if the lower bound of the 95% CI around the observed effect in Cohort 3, TC3/IC3 subgroup exceeds the upper bound of the 95% CI observed with nivolumab for the second-line treatment of squamous NSCLC, with ramucirumab plus docetaxel for second-line treatment of non-squamous NSCLC or with available therapy for third line NSCLC.

2. If data from BIRCH and supportive data from POPLAR, FIR, and Study PCD4989g support a positive benefit/risk for the PD-L1–selected intent-to-treat (ITT) population in BIRCH, TC2/3 or IC2/3, does the Agency then agree that this data could support AA in previously treated NSCLC per 21 CFR part 601, subpart E in this population?

FDA Response: Please see FDA response to Question # 1.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 2: Genentech acknowledged FDA's feedback.

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

3. The Sponsor proposes to use the PD-L1 IHC TC2 or IC2-selected enrollment population from BIRCH to support a PMA of a stepwise TC2 to IC2 algorithm to identify this population. Does the Agency agree with this approach?

FDA Response: FDA does not object to use of the PD-L1 IHC TC2 or IC2-selected population from BIRCH to support a PMA, where a stepwise TC2 to IC2 algorithm is used to identify this population; however, FDA is concerned that the original scoring criteria used in BIRCH and the proposed new step-wise scoring algorithm may be different. Please comment.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 3: Genentech would like to clarify that the scoring and cutoff criteria for the selection of patients at the TC2 or IC2 cutoff in BIRCH are identical to the scoring and cutoff criteria for the TC2 to IC2 stepwise algorithm. See below for BIRCH scoring criteria:

Tumor Cell (TC) PD-L1 Staining Assessment

<u>Membrane staining assessment (percentage of viable tumor cells with discernible PD-L1 membrane staining of any intensity) as % of the total number of viable tumor cells</u>	<u>>5% (TC 2/3)</u> <u><5% (TC 0/1)</u>
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Immune Cell (IC) PD-L1 Staining Assessment

<u>PD-L1 diagnostic assessment (based on the percentage of the tumor area occupied by immune cells with discernible PD-L1 staining of any intensity)</u>	<u>>5% (IC 2/3)</u> <u><5% (IC 0/1)</u>
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PD-L1 Status

<u>PD-L1 Status</u>	<u>POSITIVE</u> <u>(TC 2/3 or IC 2/3)</u> <u>NEGATIVE</u> <u>(TC 0/1 and IC 0/1)</u> <u>Not Evaluable</u>
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The stepwise scoring approach was developed based on pathologist feedback as a useful approach to scoring TC2 or IC2 to aid in the pathologist's workflow.

Discussion during the meeting: Genentech confirmed that samples will not be re-scored or re-stained for TC 2/3 or IC 2/3 in the BIRCH Study. Genentech has not determined if the assay will be validated for PD-L1 negative population of TC 0/1 and IC 0/1.

4. Does the Agency agree with the proposed SCE/ISE SAP regarding integration of efficacy data in the NSCLC BLA across BIRCH, POPLAR, FIR, and Study PCD4989g (NSCLC cohort)?

FDA Response: FDA does not object to conducting the proposed pooled efficacy analyses of ORR and DOR across BIRCH, POPLAR, FIR, and Study PCD4989g. However, the SCE/ISE of the proposed BLA should also include a summary of the results of each study per the respective protocols and SAPs. The proposed plan for pooling data in the SCE/ISE should include a discussion on key differences in the demographics and enrollment characteristics of the pooled efficacy population (i.e., BIRCH, POPLAR, FIR, and Study PCD4989g).

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 4: The Sponsor would like to confirm that the pooled analyses as well as a summary of results of each study per respective protocols and SAPs (See Section 1 in the SCE/ISE SAP), including a discussion on key differences in the demographics and enrollment characteristics will be in the SCE/ISE (See Section 2.2.2 in the SCE/ISE SAP).

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

5. Does the Agency agree with the proposed SCS/ISS SAP regarding integration of safety data in the NSCLC BLA across BIRCH, POPLAR, FIR, and Study PCD4989g (NSCLC cohort)?

FDA Response: FDA generally agrees with the proposed SCS/ISS analysis plan pooling data from FIR, POPLAR, BIRCH, and Study PCD4989g in addition to the study-level safety analyses performed separately for each of the studies as specified in each study-specific SAP. However, in addition to the proposed plan, in the SCS/ISS analysis, Genentech should include detailed information on immune-related adverse events defined as any adverse event requiring the use of corticosteroids with no clear alternate etiology. Information on immune-related adverse events should include time to onset of event, time to start of corticosteroids/other immunosuppressive agents, dose of corticosteroids/other immunosuppressive agents, duration of corticosteroids or other immunosuppressive agents treatment, adverse event outcome, and duration of event from onset until documented resolution.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 5: Genentech acknowledges the Agency's feedback. The AE and concomitant medication CRF in the NSCLC studies are not set up to link steroid use with immune-related AEs. Genentech proposes the submission of line listings for the information requested above for each individual study. Does the Agency agree with this proposal?

Discussion during the meeting: FDA stated that the line listings containing AE data, Immune-mediated AEs, and concomitant medications, including corticosteroids for each individual study should be relatively straight-forward to generate from existing datasets. FDA requested that a separate dataset be submitted for immune-mediated adverse events per FDA's definition. Genentech agreed to provide this data.

6. Does the Agency agree with the proposed SAP for POPLAR?

FDA Response: The OS analysis based on approximately 150 deaths was pre-specified as the final OS analysis in the original design. In this version of SAP, the OS analysis based on approximately 150 deaths (occurred on January 30, 2015) is changed from pre-specified final analysis to the third interim analysis and the final OS analysis is modified to be conducted based on 180 deaths. FDA considers the OS analysis based on approximately 150 deaths as the final OS analysis. However, FDA does not object to an additional exploratory analysis based on approximately 180 deaths.

As Genentech stated in the SAP (2.3) 'This Phase II study is designed to provide an initial assessment of the efficacy and safety of MPDL3280A, and the primary purpose is the estimation of the OS and PFS hazard ratios in the PD-L1–selected subset and in the overall population (ITT).' Therefore, FDA considers OS, PFS and other efficacy analyses results in subgroups to be supportive or exploratory.

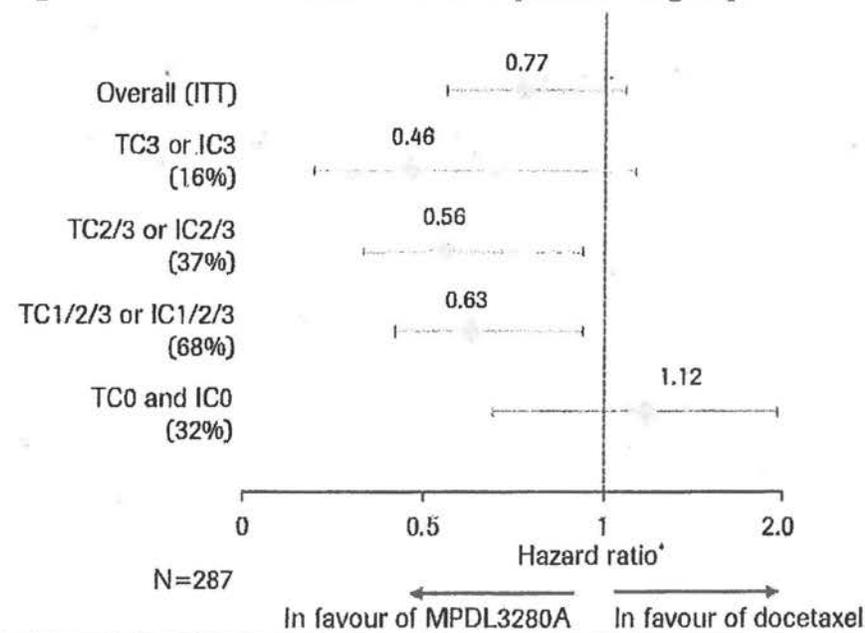
Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 6: Genentech acknowledges that FDA considers the OS analysis based on approximately 150 deaths as the final POPLAR analysis. Genentech plans to provide the OS analyses of 150 deaths and 180 deaths in the BLA submission.

Genentech would like to explore with the Agency the role of POPLAR overall survival data as it provides an important clinical benefit for 2L+ NSCLC patients for this breakthrough designated product. Key considerations include:

- OS is a direct measure of clinical benefit as compared to PFS or ORR
- Interim analyses were pre-specified in the POPLAR protocol
- Observed numerical gradient effect of OS in the PD-L1 expression subgroups in POPLAR (See Figure 1)
- OS benefit appears to extend to subgroups with lower PD-L1 expression, with improved benefit with increasing PD-L1 expression (refer to mutually exclusive subgroup analyses in Table 9 in the pre-meeting package)
- Consistent data has been observed in lung studies, including PCD4989g, FIR, and POPLAR

- OAK is intended to confirm the OS results with pre-specified hypothesis testing in biomarker subgroups defined by the same cut-offs
- OAK is currently fully enrolled (n=1225, data availability is approximately January 2017)

Figure 1: POPLAR OS data in PD-L1 expression subgroups



Discussion during the meeting: FDA stated that the data from the POPLAR Study would be useful in supporting a request for accelerated approval but not an application seeking traditional approval. FDA also stated that the survival data likely would not be included in product labeling except perhaps in a qualitative fashion to describe results in sub-groups who may not benefit from treatment. FDA agreed to discuss a proposal to revise the statistical analysis plan SAP for the OAK study to include a plan for interim analysis of OS which might be submitted to support proposed the initial BLA. The utility of these data to support the BLA and labeling claims would depend on the results observed at the interim analysis of OS in OAK.

7. Does the Agency agree with the proposed plan for submitting narratives for the NSCLC BLA for the following studies of BIRCH, POPLAR, FIR, and PCD4989g?

FDA Response: Yes, FDA generally agrees with the proposed plan for submitting patient narratives in Studies BIRCH, POPLAR, FIR, and PCD4989g. However, in the proposed BLA submission, Genentech must include patient narratives for all cases of immune-mediated adverse reactions as defined in FDA's response to Question # 5 in addition to adverse events of special interest as defined by Genentech's pre-specified MedDRA preferred terms.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 7: Genentech acknowledges the Agency's feedback and proposes to provide narratives for patients who received systemic steroids for immune-mediated adverse reactions. Does the Agency agree with this proposal?

Discussion during the meeting: FDA stated that Genentech's proposal to provide narratives for patients who received systemic corticosteroids for treatment of immune-mediated adverse reactions is acceptable.

8. The Sponsor's current filing plans include the submission of the MPDL3280A BLA for bladder cancer one month prior to submission of the planned BLA for treatment of NSCLC. Module 3 and Module 4 will remain unchanged between the two BLAs. Does the Agency agree that the Sponsor may cross refer to Module 3 and Module 4 from a previously submitted UBC BLA in the NSCLC BLA?

FDA Response: Genentech's proposal appears reasonable. Please note, that the responses to the questions posed in this meeting are preliminary and should be re-visited during the formal pre-BLA meeting to reach agreement under the PDUFA V Program.

Genentech's May 11, 2015, electronic (email) communication to FDA's preliminary response to question # 8: Genentech acknowledges the Agency's feedback.

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

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.

FDA acknowledges receipt of Genentech's Agreed Initial Pediatric Study Plan (iPSP) submitted on February 6, 2015 and also refers to FDA's letter, dated May 8, 2015, confirming FDA's agreement with the iPSP. This fulfills Genentech's requirements at this stage of development to reach an Agreed iPSP with the Agency, as required by FDASIA for products that would trigger PREA at the time of BLA submission.

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