CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 138735

MEETING MINUTES

Mirati Therapeutics, Inc.
Attention: Allen Albright, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
3545 Cray Court
San Diego, CA 92121

Dear Dr. Albright:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MRTX849.

We also refer to the meeting between representatives of your firm and the FDA on November 17, 2021. The purpose of the meeting was to align on Mirati's plans for submission of a New Drug Application for MRTX849 for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation (b) (4).

A copy of the official minutes of the meeting/telecon 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 240-402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for Division of Oncology 2
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 17, 2021, 12:00PM – 1:00PM, EST
Meeting Location:	Teleconference
Application Number:	IND 138735
Product Name:	MRTX849
Indication:	for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.
Sponsor:	Mirati Therapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Paz Vellanki
Meeting Recorder:	Opeyemi Udoka

FDA ATTENDEES

Martha Donoghue, M.D., Deputy Director, Division of Oncology 2 (DO2)
Paz Vellanki, M.D., Ph.D., Cross Disciplinary Team Leader, DO2
Katie Chon, Pharm. D., Clinical Reviewer, DO2
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCPII)
Blaire Osborn, Ph.D., Clinical Pharmacology Reviewer, DCPII
Claudia Miller, Ph.D., Acting Non-Clinical Team Leader, Division of Hematology, Oncology, and Toxicology (DHOT)
Amy Skinner, Ph.D., Non-Clinical Reviewer, DHOT
Pallavi Mishra-Kalyani, Ph.D., Biostatistics Team Leader, Division of Biostatistics (DBV)
Timothy Schaefer, Ph.D., Scientific Reviewer, Center for Devices and Radiological Health (CDRH)
Opeyemi Udoka, D.P.T., Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

Allen Albright, Ph.D., Vice President, Regulatory Affairs and Quality Assurance
Greg Stevens, Ph.D., Toxicologist, Consultant
James Christensen, Ph.D., Executive Vice President, Chief Scientific Officer
Jonathan Tran, Pharm.D., Vice President, Clinical Pharmacology and Nonclinical Development
Joseph Leveque, M.D., Executive Vice President, Chief Medical Officer

Kenna Anderes, Ph.D., Vice President, Translational Medicines and Companion Diagnostics
Lauren Kattus, M.S., R.A.C., Associate Director, Regulatory Affairs and Operations
Peter Olson, Ph.D., Senior Director, Research
Richard Chao, M.D., Vice President, Innovative Medicines
Sharon Real, Ph.D., Vice President, Regulatory CMC
Susan Welsh, M.B., Ch.B., Senior Vice President, Pharmacovigilance/Chief Safety Officer
Thian Kheoh, Ph.D., Vice President, Biometrics
Vincent Caralli, Senior Director, Regulatory Affairs
William Bleker, M.D., Executive Director, Pharmacovigilance & Safety Risk Management
Xiaohong Yan, Ph.D., Senior Director, Biostatistics

BACKGROUND

On September 24, 2021, Mirati Therapeutics, Inc. (Mirati) submitted a meeting request to align on their plan for submission of a New Drug Application (NDA) for MRTX849 for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.

The meeting package was received on October 18, 2021.

Regulatory

On May 20, 2020, Fast Track designation was granted for MRTX849 for the treatment of patients with histologically confirmed, metastatic *KRAS* G12C mutated non-small cell lung cancer (NSCLC) (b) (4)

On September 2, 2020, Mirati had an End of Phase 1 (EOP1) CMC meeting to gain Agency agreement on the proposed strategies for (b) (4) in the drug substance and justifying the appropriateness of the proposed drug substance (b) (4) ; the proposed drug substance and drug product analytical control strategies; and the acceptability of the proposed drug substance and drug product registrational stability programs.

On May 10, 2021, an agreed initial pediatric study plan was issued describing a planned request to seek a full waiver from the requirements of Pediatric Research Equity Act (PREA) for all pediatric age groups in an application for marketing approval for MRTX849 for patients with histologically confirmed, advanced or metastatic *KRAS* G12C-mutated NSCLC (b) (4)

On June 16, 2021, Mirati submitted a meeting request to obtain feedback and agreement on the proposed formulation bridging strategy and developmental and registrational CMC plans for MRTX849 capsule and tablet. FDA issued preliminary comments on August 24, 2021. Upon receipt of the preliminary comments, the meeting was cancelled on August 30, 2021.

On June 23, 2021, Breakthrough therapy designation was granted for MRTX849 for the treatment of patients with histologically confirmed, advanced or metastatic *KRAS* G12C mutated NSCLC (b) (4)

On October 5, 2021, Mirati submitted a request for participation in the Real-Time Oncology Review (RTOR) pilot program based on top line results from Study 849-001 Cohort A.

On October 29, 2021, Mirati submitted the first component under RTOR New Drug Application for NDA 216340 with the last component expected on December 14, 2021.

Nonclinical

Mirati is developing MRTX849, a small molecule kinase inhibitor that is active against the KRAS G12C mutation for treatment of patients with NSCLC harboring a KRAS G12C mutation. Mirati has conducted a series of pharmacology, pharmacokinetic (PK), and ADME studies, as well as a stand-alone GLP-compliant dog telemetry cardiovascular study, and a hERG assay. Mirati also completed up to 13-week, repeat-dose, GLP-compliant toxicology studies in rats and dogs. Mirati completed embryo/fetal development studies in rats and rabbits. Finally, Mirati evaluated potential toxicity of three impurities in separate 4-week, repeat-dose, GLP-compliant toxicology studies. Two of those studies are complete, and one is ongoing. As we recommended in the preliminary meeting comments on January 28, 2020, Mirati completed a GLP-compliant in vivo genotoxicity study and an in vitro phototoxicity study.
In a prior email communication on October 7, 2021, FDA agreed that Mirati can submit draft reports of 28-day rat GLP toxicity studies evaluating an impurity and GLP hERG study evaluating two metabolites within the planned December 10 NDA submission provided that final reports and SEND datasets will be submitted in January, along with a summary of changes from the draft reports.

Clinical

Study 849-001 (KRYSTAL-1) is an ongoing, first-in-human, multicenter, dose escalation, dose expansion trial of MRTX849 in patients with advanced solid tumors with KRAS G12C mutations for which there is no curative treatment. For the Phase 1 dose escalation and the cohort sub-studies, patient eligibility for malignancies with KRAS G12C mutations was assessed using Mirati-approved local or central laboratory tests. In the Phase 2 dose expansion cohorts, tumor tissue and/or blood samples were

required for either prospective or retrospective central laboratory testing. The primary objective of the dose escalation portion of the study was to assess the safety and tolerability, PK, establish the maximum tolerated dose (MTD), and identify the recommended phase 2 doses (RP2Ds) of MRTX849. The dose escalation part of the study is completed and the MRTX849 dose of 600 mg twice daily (BID) was selected to be further studied in Phase 2 expansion cohorts. The primary endpoint for the Phase 2 cohorts is objective response rate (ORR). The following expansion cohorts are included in the study, with Cohort A intended to provide the main efficacy and safety results to support the proposed NDA submission for accelerated approval:

- Cohort A: patients with advanced NSCLC with KRAS G12C mutation detected in tumor tissue, with prior treatment with platinum-based chemotherapy and an immune checkpoint inhibitor (n = 116, including four patients without measurable disease at baseline per RECIST as assessed by central review)
- Cohort B: patients with NSCLC with KRAS G12C mutation detected in blood (i.e., ctDNA) (n = approximately 40)
- Cohort C: patients with colorectal cancer (CRC) with KRAS G12C mutation detected in tumor tissue and/or blood (n = approximately 40)
- Cohort D: patients with other solid tumors with KRAS G12C mutation detected in tumor tissue and/or blood (n = approximately 60)
- Cohort E: patients with NSCLC with KRAS G12C mutation and STK11 comutations detected in tumor tissue and/or blood in the first-line systemic treatment setting (n = approximately 65)
- Cohort F: patients with CRC with KRAS G12C mutation detected in tumor tissue who have previously received a fluoropyrimidine, oxaliplatin, irinotecan and a VEGF/VEGFR inhibitor that is FDA-approved for treatment of CRC, and have progressed during or within 3 months of the last administration of chemotherapy (n = approximately 40)
- Cohort G: patients with CRC with KRAS G12C mutation detected in tumor tissue (n = approximately 60)

For Cohort A, the primary analysis was objective response rate (ORR) by blinded independent central review (BICR) per RECIST v1.1 and used the Clopper-Pearson exact methodology to calculate the 95% CI. Assuming an actual response rate of 35%, a sample size of 105 patients was planned so that the lower limit of the 95% CI would be higher than 23%.

Genotyping of tumor tissue and/or ctDNA for the KRAS G12C mutation were used to determine patient eligibility for the trial. If tumor tissue samples were not available for assessment of eligibility into Cohort A, patients were prospectively enrolled into Cohort B based on a plasma-based test. Mirati indicated they intend to submit a sPMA for the Resolution ctDx first assay (estimated submission December 2021) and for the Qiagen therascreen KRAS RGQ PCR Kit (estimated submission January 2022).

Summary of efficacy
Based on a data cutoff date of June 15, 2021, 116 patients with squamous or non-squamous NSCLC harboring the KRAS G12C mutation in tumor tissue, and who were previously treated with at least a platinum-containing chemotherapy regimen and an anti-PD-(L)1 antibody, were enrolled into Cohort A and received MRTX849 600 mg BID. All patients were documented to have the KRAS G12C mutation in tumor tissue according to local laboratory testing with 109 patients (94%) enrolled based on results from next generation sequencing (NGS), 4 patients (3.4%) enrolled based on polymerase chain reaction (PCR) testing, and 3 patients (2.6%) enrolled based on Sanger sequencing.

Although 116 patients were enrolled to Cohort A, only 112 patients had measurable disease at baseline per RECIST v1.1, as evaluated by BICR. Of the 116 patients, 82 (71%) received prior treatment with concurrent platinum-based chemotherapy and an anti-PD-(L)1 antibody. Seventy-six (66%) of patients discontinued MRTX849 therapy and 40 (34%) patients were still ongoing at the time of the data cutoff date. A summary of the efficacy results is provided in the table below.

Efficacy Endpoint	Cohort A N=112
ORR by BICR, % (95% CI) Complete response, n Partial response, n	43% (34, 53) 1 47
Median DOR (mos) 95% CI % responders with response ≥ 6 mos	7.3 5.1, NE 35

NE: not estimable

Summary of Safety

All patients in Cohort A of Study 849-001 experienced treatment-emergent adverse events (TEAE); the most common TEAEs reported (≥ 20% of patients) were diarrhea (69%), nausea (69%), fatigue (59%), vomiting (56%), dyspnea (35%), peripheral edema (28%), constipation (22%), and dizziness (21%). Serious adverse events (SAE) were reported in 70 patients (60%) with pneumonia reported in 11% and dyspnea reported in 9%.

TEAEs led to dose reduction or interruptions in 95 patients (82%) and permanent discontinuation of MRTX849 in 17 patients (15%). Grade 3 or 4 hematology laboratory abnormalities occurring on-treatment in at least 10% of patients were decreased lymphocyte count (29%). Grade 3 or 4chemistry laboratory abnormalities occurring on-treatment in at least 5% of the patients were hyponatremia (8%), increased AST (6%), and increased ALT (5%). No Hy's Law cases were reported. Prolonged QTcF > 500 ms

was reported in 9% of patients, and 15% of patients had QTcF change from baseline of > 60 ms.

The proposed contents of the NDA include the following:

- The SCE will contain efficacy data collected in Study 849-001, Cohort A along with supportive clinical activity data collected in patients with NSCLC with KRAS G12C mutation who received MRTX849 600 mg BID in the dose escalation or Phase 2 Cohort B in Study 849-001. An Integrated Summary of Efficacy (ISE) will also be included in the submission containing top-line efficacy results from all cohorts from Study 849-001, including patients with tumors other than NSCLC.
- Mirati proposes to present pooled safety data for a total of 265 patients from Study 849-001, including all patients with NSCLC (n=188) who received MRTX849 600 mg BID across both the dose escalation and dose expansion parts, 46 patients with CRC, and 26 patients with other solid tumors. Of the 265 patients, 260 received MRTX849 600 mg BID and 5 patients received MRTX849 once daily dosing regimens (i.e., 150 mg daily [QD], 300 mg QD, 600 mg QD, or 1200 mg QD). The Integrated Summary of Safety (ISS) document will refer to Section 2.7.4 for the narrative text while also providing a brief orientation to the tables, figures, listings and datasets provided within the ISS.

(b) (4) Mirati has an ongoing confirmatory Study 849-012, in patients with metastatic NSCLC with KRAS (p.G12C) mutation after treatment with platinum-based chemotherapy and an anti-PD-(L)1 antibody. On August 10, 2021, Mirati requested a Written Responses Only (WRO) meeting on the following proposed changes to the study:

- Allowance of crossover from the docetaxel arm based on investigator-assessed disease progression.
- Revision of the dual primary endpoints of progression-free survival (PFS) by BICR and overall survival (OS), to PFS by BICR as the primary endpoint and OS as the secondary endpoint.
- Re-sizing of the sample size to characterize the revised primary endpoint.
- Potential to use external patient data to support data from the randomized control group.

Please refer to the October 21, 2021 WRO meeting minutes for additional details and FDA responses. On October 29, 2021, Mirati indicated there are 5 patients randomized and 51 active sites for Study 849-012.

Clinical Pharmacology

MRTX849 is an orally available, covalent inhibitor that binds to the cysteine residues of KRAS G12C. It has a mean half-life of 23 hours, and there is significant drug accumulation (5 - 6-fold) when dosed BID. In a human mass balance study, after a 600-

mg dose, the geometric mean cumulative recovery of radioactivity over the collection period (0 to 504 hours) was 79.2%. MRTX849 is primarily eliminated via the fecal route (~75%), with an additional 4.5% eliminated in urine. Only 1.8% of the dose was excreted unchanged in urine, indicating a limited role for renal clearance of MRTX-849 . When administered with a high fat meal, AUC_{inf} and C_{max} were 1.38- and 1.20-fold higher than when MRTX849 was administered under fasted conditions, respectively.

MRTX849 shows a substantial number of drug-drug interactions. Concomitant use of a proton pump inhibitor (PPI) decreased MRTX849 exposure by 38% (C_{max}) and 32% (AUC). Use of strong CYP3A4 inhibitors increased MRTX849 C_{max} by 2.4-fold and AUC by 4-fold. According to Mirati, at steady-state the impact is predicted to be minimal in patients because of the extent of auto-inhibition by MRTX849. Dosage adjustments for MRTX849 during co-administration with CYP3A4 inhibitors may not be warranted.

Strong CYP3A4 inducers should be avoided as rifampin was shown to reduce MRTX849 C_{max} by 88% and AUC by 95% in healthy subjects. Concurrent administration with other CYP3A4 substrates may result in increased exposure of the co-administered substrate drug. Use of narrow therapeutic index CYP3A4 substrates should be avoided or the dose of the co-administered substrate reduced. Similarly, use of sensitive CYP2C9 and CYP2D6 substrates should be avoided, or the dose of the substrate drugs should be reduced.

No dosage adjustment for MRTX849 is needed in subjects with mild, moderate, or severe renal impairment. This is expected based on the limited role of renal elimination for drug excretion. Data on the impact of moderate or severe hepatic impairment will not be available for this NDA submission.

Finally, increasing MRTX849 concentrations are associated with clinically relevant QTc prolongation in patients.

FDA sent Preliminary Comments to Mirati on November 15, 2021. On November 16, 2021 Mirati provided responses and requested to further discuss questions 2, 6, 6d, and FDA comment 20 in that order of priority.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that the nonclinical package is sufficient to support the NDA submission?

   FDA Response: The completed nonclinical studies described in your meeting package appear sufficient to support a marketing application. A final determination of the adequacy of the nonclinical data will be made after

reviewing the NDA submission.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

2. Does the FDA agree that the Clinical Pharmacology package is adequate and key conclusions are sufficient to support the NDA submission?

FDA Response: When complete, the proposed clinical pharmacology package appears sufficient to support the planned NDA. It is noted that some studies remain incomplete (849-003) and there are limited available data on the impact of hepatic impairment. FDA expects that there will be adequate data to fully assess the impact of hepatic impairment prior to approval. As the available data are limited, the acceptability will remain a review issue.

The planned exposure-response analysis appears acceptable. A final determination of the adequacy of the clinical pharmacology package will be assessed at the time of NDA review.

Further, FDA continues to have concerns regarding the selection of the dose for use in these trials. The MRTX849 600 mg BID dosage appears tolerable and has shown some efficacy, however, it remains the only dose to have been evaluated on the BID schedule.

We acknowledge your recent submission of protocol version 9.0 for Study 849-001 and your plans to include a cohort of patients with NSCLC who will receive MRTX849 400 mg BID with or without food. Any comments regarding this protocol amendment will be provided in a separate communication. Clarify when you anticipate data from patients treated with the 400 mg BID dose and when this will be submitted to the FDA.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges these comments and would like to clarify the following:

- Study 849-003 (PK in subjects with mild, moderate, and severe hepatic impairment) has completed the clinical conduct and data analysis is ongoing. The final clinical study report (CSR) is expected on 16 February 2022. Mirati plans to submit the CSR to the NDA by 18 February 2022. Does the FDA agree that Mirati can submit the 849-003 CSR during the NDA review to support approval and labeling?
- Based on current enrollment projections for the 400 mg BID cohort in Study 849-001 (n=30), preliminary PK, safety, and efficacy results from patients treated with the 400 mg BID dose for submission are anticipated

at the end of 4Q 2022. Safety and efficacy data with sufficient follow-up are anticipated in 2Q 2023 for a study report by the end of 2023.

Discussion During the 11/17/21 Teleconference:
FDA agreed that submission of the CSR for 849-003 to the NDA by 18 February 2022 would be acceptable. A summary of 849-003 results should be added as an addendum to the summary of clinical pharmacology in module 2. FDA confirmed that labeling will be updated based on the results of this trial, provided that they are submitted by the agreed-upon date.

Although it is not optimal that submission of data from the 400 mg BID cohort will occur in 2023, FDA indicated that this is acceptable. Mirati should provide an update on the enrollment status for the 400 mg BID cohort by March or April of 2022.

3. On the assumption that Mirati will participate in the Real-Time Oncology Review (RTOR) program for the planned NDA, could the FDA prioritize the review of the BE data that will be provided by 24 November 2021, as outlined below? Mirati would appreciate an assessment on the FDA's acceptance of the adequacy of the bioequivalence study results supporting the commercial tablet formulation as a commercial dosage form by 15 January 2022 ahead of the anticipated NDA filing date of 15 February 2022.

FDA Response: Under the RTOR program, FDA can prioritize review of these data. However, a final determination regarding the adequacy of the data may not be possible until the complete clinical pharmacology data package has been reviewed.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

4. Does the FDA agree with the proposed indication statement?
MRTX849 is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.

FDA Response: A determination regarding the indication statement will be made upon review of your NDA submission.

We note that in the study, baseline plasma samples were collected from all enrolled patients in Cohort A to enable analysis with a companion diagnostic for an sPMA for a plasma-based assay. For the tissue-based assay, we note the protocol reflects the central laboratory as (b) (4) for tumor

tissue, using PCR for eligibility testing. We reference the February 3, 2020, meeting in which you indicated your plans to (b) (4) ; however, more recently in your RTOR request, you indicated that you intend to submit an sPMA for the Qiagen therascreen KRAS RGQ PCR test for your tissue-based assay instead. Clarify your plans, including the assays and timeline, for your sPMA submissions.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and would like to clarify the sPMA submission plans:

Study 849-001 allowed Cohort A eligibility based on sponsor-approved local and commercial testing using next generation sequencing, PCR, or Sanger-based sequencing platforms. The primary companion diagnostic strategy for Cohort A is to perform a tumor tissue-based bridging concordance analysis based on CDRH Guidelines for eligibility testing and the planned companion diagnostic test for all available and evaluable baseline tumor tissue samples for enrolled patients to enable a supplemental PMA submission by Qiagen for the therascreen KRAS RGQ PCR kit. Qiagen will submit a supplemental PMA for the therascreen KRAS RGQ PCR kit in January 2022.

In addition, baseline plasma samples were collected for all Cohort A patients who were eligible and were enrolled based on sponsor-approved local and commercial testing to enable a second PMA submission for a plasma-based ctDNA companion diagnostic. For the plasma-based ctDNA assay, Resolution Bioscience will submit a new PMA for the Resolution ctDx FIRST NGS assay in December 2021, including information on MRTX849 cohort A to support companion claims.

Written feedback to Pre-Submission requests for both Qiagen (ref. Q202272/S001) and Resolution Bioscience, Inc (ref. Q201818) have been previously received from CDRH.

(b) (4)

Discussion During the 11/17/21 Teleconference: No discussion occurred.

5. Does the FDA agree that no Med guide or REMS will be necessary to support the submission and approval of the NDA?

FDA Response: The necessity of a medication guide or REMS will be

determined during the NDA review.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

6. Does the FDA agree with both the proposed pooled safety population (including plans for pooling, display, and narrative text placement) and the proposed presentation of patient narratives?

FDA Response: The proposed pooled safety population is mostly acceptable. However, data from the five patients who received alternative dosage regimens of MRTX849 should be not pooled with data from the other 260 patients who received MRTX849 600 mg BID; safety data from the five patients should be presented separately.

In addition, provide separate pooled safety data for only the lung cancer patients who received MRTX849 600 mg BID.

Safety narratives should be provided for all deaths within 30 days of last dose of study treatment, for any pregnancy or overdose occurring on study, serious adverse events, and all events leading to study discontinuations.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment and would like further discussion on this comment. Based on the recommendations outlined in the Type C Meeting (Written Responses Only, received 15 July 2021, Reference ID: 4652405), Mirati planned to pool safety data from all patients who received MRTX849 as a single agent at the intended dose of 600 mg BID; these plans were reiterated in email correspondence received 23 Sep 2021 when Mirati sought further guidance on combination safety data. Based on these correspondences, Mirati has finalized the statistical analysis plan for the integrated summary of safety and has generated the ISS tables that include pooling for all patients treated at an assigned dose of MRTX849 600 mg BID regardless of tumor type. Mirati understands the value of pooled safety data for lung cancer patients who received MRTX849 600 mg BID but also considers pooling across tumor types as representative of the safety profile. Mirati requests discussion if the current pooling strategy (including all patients treated at MRTX 600 mg BID regardless of tumor type) may be retained.

Discussion During the 11/17/21 Teleconference: FDA stated that Mirati should provide separate pooled safety data for patients with NSCLC dosed at 600 mg BID to help identify safety signals specific to the population of patients with lung cancer. Mirati should include a tabular comparison of adverse events and additionally provide an assessment of any differences in safety between the

overall population and the population of patients with NSCLC. If necessary, Mirati may provide this data as an addendum to the NDA at the time of submission of the 120-day update, or earlier if possible.

a. Mirati proposes to summarize the all-causality SAEs that have been reported with these combinations for an assessment of unique safety signals with these agents in response to email correspondence with the Agency sent 23 September 2021 requesting Mirati provide an assessment regarding whether there are any unique safety signals that arose in the patients receiving combination treatment. Does the Agency agree?

FDA Response: Your proposal to summarize all-causality serious adverse events for MRTX849 administered in combination with pembrolizumab, cetuximab, afatinib, TNO155, BI 1701963, and palbociclib to evaluate any unique safety signals appears reasonable.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

b. Does the FDA agree with planned data to be included in the NDA submission for the evaluation of QT are acceptable?

FDA Response: A response to this question will be provided as a post-meeting addendum.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

c. Does the FDA agree with the proposed safety population for summarizing the adverse reactions in Section 6.1 of the draft USPI?

FDA Response: We agree with your proposal to include Cohort A patients in Section 6.1 to inform product labeling. Since the trial is a single arm cohort, treatment emergent adverse events will be reported as adverse reactions in the USPI, unless they are unequivocally attributed to an alternate etiology (e.g., injury due to a car accident).

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges

this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

d. Does the FDA agree with the proposed safety population and format for summarizing the 120-day safety update?

FDA Response: We do not agree with your approach to exclude patients in the ongoing trials, Study 849-012 and Study 849-007, from your 120-day safety update. In addition, you should provide safety data from Study 849-EAP-001. Any new safety information learned about MRTX849 that may reasonably affect the statement of warnings and precautions must be submitted to a pending NDA.

Clarify when you plan to submit your 120-day safety update based on a data cutoff date of October 15, 2021.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment and would like further discussion at the teleconference. Mirati plans to submit the 120-day update in mid-March, 2022, using a data cutoff date of 15 Oct 2021. Mirati proposes to include patients receiving single agent MRTX849 as shown in the following table.

Table 1: Patients Receiving Single Agent MRTX849 Proposed for Inclusion in the 120-Day Safety Update

	ISS Cutoff Date	N (ISS)	120-Day Safety Update Cutoff Date	N (120-Day Safety Update)
Study 849-001, Phase 1/1b	27NOV2020	25	15OCT2021	25
Study 849-001, Cohort A	15JUN2021	116		116
Study 849-001, Cohorts B, C, D	15JUN2021	124		~147
Study 849-001, Other Phase 1b Monotherapy	N/A	N/A		~40
Study 849-001, Other Phase 2	N/A	N/A		~39
Study 849-007, MRTX849 Single Agent Arm	N/A	N/A		~0
Study 849-012, MRTX849 Arm	N/A	N/A		~4
Study 849-EAP-001	N/A	N/A		~0
Total		265		371

Mirati also proposes to use the following format to summarize the frequencies of adverse events reported with monotherapy treatment in the 120-day safety update, including a separate group for NSCLC patients from Phase 1/1b dose-finding, Cohorts A and B, and patients randomized to MRTX849 in Study 849-

012:

Table 2: Proposed Format to Summarize AE Frequency (Monotherapy) in the 120-Day Safety Update

Adverse Event (n (%)) (System Organ Class/Preferred Term)	**MRTX849 600 mg BID**			Other Dosing Regimens[3] (n~5)
	NSCLC[1] (n~196)	Other[2] (n~170)	Total (N~366)	

1. From Study 849-001 (Phase 1/1b [Dose Finding, n=16], Cohort A [n=116], and Cohort B [n=60]) and Study 849-012 (patients randomized to MRTX849, n=4)
2. From Study 849-001 (Phase 1b [not part of dose finding], and Phase 2 Cohorts C, D, E, and F), Study 849-007 (monotherapy arm), and Study 849-EAP-001.
3. Other dosing regimens include 150 mg QD, 300 mg QD, 600 mg QD and 1200 mg QD.

As planned for the SCS (as described in Question 6a), Mirati proposes to use the safety database to provide an update of the all-causality serious adverse events for MRTX849 administered in combination with pembrolizumab, cetuximab, afatinib, TNO155, BI 1701963, and palbociclib to evaluate any unique safety signals for combination treatment. The corresponding study numbers and estimated numbers of patients for each combination for a cutoff date of 15 Oct 2021 are tabulated in the table below.

Table 3: Estimated Patient Numbers for Combination Treatment in the 120-Day Update

	Pembrolizumab	**Cetuximab**	**Afatinib**	**TNO155**	**BI 1701963**	**Palbociclib**
Study 849-001, Phase 1/1b	30	38	14	N/A	N/A	N/A
Study 849-002	N/A	N/A	N/A	86	N/A	N/A
Study 849-007	44	N/A	N/A	N/A	N/A	N/A
Study 849-010	N/A	4	N/A	N/A	N/A	N/A
Study 849-014	N/A	N/A	N/A	N/A	14	N/A
Study 849-016	N/A	N/A	N/A	N/A	N/A	0
Total	74	42	14	86	14	0

Discussion During the 11/17/21 Teleconference: FDA acknowledged Mirati's response and agreed their proposal is generally acceptable. For MRTX-849 in combination with other agents, Mirati should also provide data and an assessment of any Grade 3 or higher adverse events at the 120-day safety

update. Mirati should provide an assessment as to whether they identify any new safety signals at the 120-day safety update for MRTX-849 either as a single agent or in combination with other agents. update.

e. Does the FDA agree that updated efficacy data including duration of response and objective response may be submitted with the 120-day safety update for potential inclusion in the USPI?

FDA Response: We agree with your proposal to submit efficacy data (i.e., duration of response for responders based on your cutoff date of June 15, 2021) with the 120-day safety update. The updated duration of response data, but not updated overall response rates, may be considered for inclusion in the USPI. We note that the median DOR for Cohort A is 7.3 months, but only 35% of patients had a DOR of 6 months or more. Please clarify whether all responding patients have been followed for a minimum of 6 months following onset of response.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment and would like to clarify that 17 responding patients have been followed for 6 months by the data cut off of June 15, 2021. All the responding patients will have 6-month follow-up by Oct 15, 2021, the data cut off for the 120-day safety update.

Discussion During the 11/17/21 Teleconference: FDA previously indicated that the NDA submission should occur after all responders in Cohort A of Study 849-001 have at least 6 months of follow-up post onset of response. Mirati indicated that as of the June 15, 2021 data cutoff date, only 17 out of 48 (35%) responders have at least 6 months of follow-up post onset of response. Mirati also indicated that all responders will have at least 6 months of follow-up post onset of response at the October 15, 2021 data cutoff date.

FDA clarified in order to make a determination with respect to the fileability of the marketing application, more mature durability information would be needed. Mirati agreed to provide a proposal for a timeline for submission of durability data reflecting a timepoint after the June 2021 cut-off date in approximately one week. FDA stated this was acceptable.

f. Does the FDA agree with the location of the case report forms within the eCTD?

FDA Response: We agree with your proposal.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges

this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

7. Does the FDA agree that the 02 February 2021 agreed iPSP supports the planned submission for a full waiver from the requirements of PREA for all pediatric age groups in the NDA submission?

FDA Response: No. Reference is made to the May 10, 2021, FDA Agreed Initial Pediatric Study Plan – Agreement letter and your April 15, 2021 amended Agreed Initial Pediatric Study Plan outlining a planned request for a full waiver for all pediatric age groups. The May 10, 2021, agreed iPSP should be included in your original NDA.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment and agrees that the 10 May 2021 iPSP will be included with the original NDA. No further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

8. Does the FDA agree that Mirati can apply for Priority Review designation?

FDA Response: Your proposal is acceptable. The final decision regarding Priority Review Designation will be made upon initial review of the NDA submission.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

9. Can the FDA provide timing and extent of the BIMO inspection process for clinical sites?

FDA Response: Decisions regarding BIMO site audits are made at the time that inspections are determined to be necessary to the review of an application. We will provide advice regarding timing, scope, and processes at that time.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

10. Can the FDA provide timing and extent of the PAI process for manufacturing

sites?

FDA Response: Manufacturing sites PAI decisions are review issues and are made after the NDA is submitted.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Manufacturing sites PAI decisions are review issues and are made after the NDA is submitted.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

11. Does the FDA have an indication that an ODAC meeting will be convened for the planned NDA?

FDA Response: Based on the information contained in the background package, top line data, and considering the totality of evidence for MRTX849, we do not plan to convene an ODAC for the planned NDA at this time. A final determination will be made upon review of your application.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

12. Does the FDA agree that the covered clinical studies for which the Sponsor will submit financial disclosure information in support of the NDA will include Studies 849-001, 849-011 and 849-015?

FDA Response: Yes, we agree.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

13. Does the FDA agree with the format and content of the NDA proposed outline?

FDA Response: Yes, and include the following:

- In module 1.6.3, include the IDMC meeting minutes for Study 849-001.
- In module 5.3.5.2, include the BICR charter for Study 849-001.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference. The

requested documents will be included in the original NDA submission.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

ADDITIONAL FDA COMMENTS:

Clinical

14. The overall response rate (ORR) by blinded independent central review (BICR) for patients enrolled to Cohort A of Study 849-001 was 43% (95% CI 34, 53) and the median duration of response was 7.3 months (95% CI 5.1, NE). For Cohort B of Study 849-001, you indicate that the ORR was 16.7% (95% CI 7.9, 29.3) with DOR 4.7 months (95% CI 3.5, NE). Provide your assessment for the discrepant overall response rates between cohorts A and B.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Cohorts A and B differ primarily by the testing platform used for enrollment, with tumor tissue required for Cohort A and blood for ctDNA required for Cohort B; they also differ in that ORR has been centrally reviewed for Cohort A only. We have postulated that the ability to detect ctDNA may indicate a worse prognosis, though this factor may be less relevant for this patient population that has already received prior systemic treatment for advanced or metastatic disease. However, the primary reason for the apparently discrepant results for ORR between Cohorts A and B are the maturity of the data. Cohort A includes analysis conducted at least 6 months after the last patient-initiated treatment. The interim clinical study report for Cohort B, however, was conducted prior to full enrollment, resulting in immature data. At the time of the data cutoff for the interim clinical study report for Cohort B on 29JAN21, an additional 16.7% of patients had unconfirmed responses, all of which were subsequently confirmed. For the SCE, we have updated the safety and efficacy data for the 56 patients who had enrolled into Cohort B as of 29JAN2021 to an updated cutoff date of 15Jun2021. With the updated data, the ORR for Cohort B by investigator assessment is 42.9% (95% CI: 29.7, 56.8), which is consistent with the ORR observed in Cohort A.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

Clinical Pharmacology

15. Comments regarding justification of the selected 600 mg BID dose have been provided previously. A dose justification of the 600 mg BID dose was submitted in June of 2021. No other doses have been evaluated on the BID schedule and justification for the dose selection remains to be addressed. Provide an update on the availability of the data from the 400 mg BID dosing cohort in 849-001.

Mirati Therapeutics, Inc's Email Response on 11/16/21: The timing for the data from the 400 mg BID cohort in Study 849-001 is described in the response

to Question 2 above.

Discussion During the 11/17/21 Teleconference: No discussion occurred.

Comments for Guidance on Submission of the NDA

16. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

17. Address the following questions in the Summary of Clinical Pharmacology:
    i. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
    ii. What are the exposure-response relationships for efficacy, safety and biomarkers?
    iii. What is the effect of MRTX849 on the QT/QTc interval?
    iv. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
    v. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
    vi. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

18. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

19. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

20. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

Mirati Therapeutics, Inc's Email Response on 11/16/21:

The following tables provide guidance on the location of the flags for dose reduction, interruption, and discontinuation, and information on how to use these flags.

Table 4: PK Studies

Study	Single/ Multiple dose	PC	ADPC/ ADPP	Define document (define.xml in v2.0)	PKFL flag	DOSE reduction DOSE interruption	DOSE discontinuation
849-004	Single	Yes	Yes	Define.xml	ADSL.PKFL, ADPC.PKFL, ADPP.PKFL; and additional PP flags	NA	NA
849-005	Single	Yes	Yes	Define.xml	ADSL.PKFL, ADPC.PKFL, ADPP.PKFL; and additional PP flags	NA	NA
849-006	Multiple	Yes	Yes	Define.xml	ADSL.PKFL, ADPC.PKFL, ADPP.PKFL; and additional PP flags	NA	NA
849-011	Multiple	Yes	Yes	Define.xml	ADSL.PKFL, ADPC.PKFL, ADPP.PKFL; and additional PP flags	NA	NA
849-015	Multiple	Yes	Yes	Define.xml	ADSL.PKFL, ADPC.PKFL, ADPP.PKFL; and additional PP flags	NA	NA

Note: No subjects had dose interruption/dose reduction from dose administration perspective since dose reduction is not allowed in order to evaluate PK profile. Subjects excluded from PK analysis were flagged in ADPC/ADPP. See define.xml for details.

Table 5: Phase 1/1b and 2 Study (849-001) with PK component

Study	PC	ADPC/ ADPP	Define document (define.xml in v2.0)	PKFL flag	DOSE reduction DOSE interruption (Flag var in dataset, but at observation level)	DOSE discontinuation
849-001 CSR1	Yes	Yes / Yes	Define.xml Define.pdf	ADSL.PKFL[a], ADPC.PKFL, ADPP.PKFL	ADEX.DOSREDFL/ DOSREDRS ADEX.DOSINTFL/ DINTREAS	ADSL.EOTSTT ADSL.EOTDT ADSL.DCTREAS/ DCTREASP
849-001 CSR2[b]	Yes	Yes / No	Define.xml Define.pdf	ADSL.PKFL, ADPC.PKFL	ADEX.DOSREDFL/ DOSREDRS ADEX.DOSINTFL/ DINTREAS	ADSL.EOTSTT ADSL.EOTDT ADSL.DCTREAS/ DCTREASP

849-001 CSR3[b]	Yes	Yes / No	Define.xml Define.pdf	ADSL.PKFL, ADPC.PKFL	ADEX.DOSREDFL/ DOSREDRS ADEX.DOSINTFL/ DINTREAS	ADSL.EOTSTT ADSL.EOTDT ADSL.DCTREAS/ DCTREASP

[a] 849-001 CSR1: ADSL.PKFL is a placeholder; should not be used for PK analysis. PKFL in ADPC and ADPP can be used for PK analysis. See define.xml for details.
[b] There were no intensive pk sample collection for subjects in 849-001 CSR2/CSR3, so no pk parameter calculation, and no ADPP dataset.

APPEARS THIS WAY ON ORIGINAL

Table 6: Algorithm to derive time to first dose reduction, interruption or discontinuation; the reasons for dose Modifications

Flags/Parameters needed	Algorithm
Time to First Dose Reduction and reason	For each subject (USUBJID) in analysis dataset ADEX, select observations with DOSREDFL='Y'; among the resulting subset, then select the observation with the minimum ASTDY. If the subject has an observation, then the subject has dose reduction, and Time to First Dose Reduction is ASTDY, and reason for dose reduction is DOSREDRS.
Time to First Dose Interruption and reason	For each subject (USUBJID) in analysis dataset ADEX, select observations with DOSINTFL ='Y'; among the resulting subset, then select the observation with the minimum ASTDY. If the subject has an observation, then the subject has dose interruption, and Time to First Dose Interruption is ASTDY, and reason for dose interruption is DINTREAS.
Time to Discontinuation	For each subject (USUBJID) in analysis dataset ADSL, identify subject with EOTSTT = 'DISCONTINUED', Time to Discontinuation can be calculated as ADSL.EOTDT – ADSL.TRTSDT + 1; reason for discontinuation is in ADSL.DCTREAS/DCTREASP

Question to FDA: All studies include define.xml (v2.0). Would the define.xml in place of define.pdf meet the FDA requirement, or the define.pdf will be required in addition to the define.xml?

Discussion During the 11/17/21 Teleconference:
FDA acknowledged Mirati's response but requested that a define file be submitted in pdf and xml format. Mirati agreed.

21. Submit the following for the population pharmacokinetic analysis reports:
- Standard model diagnostic plots
- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

22. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
    - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

    Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

    Discussion During the 11/17/21 Teleconference: No discussion occurred

23. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

    Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

    Discussion During the 11/17/21 Teleconference: No discussion occurred

24. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

    Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

    Discussion During the 11/17/21 Teleconference: No discussion occurred

25. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled

terms used to inform labeling if applicable.

Mirati Therapeutics, Inc's Email Response on 11/16/21: Mirati acknowledges this comment, and no further discussion is requested at the teleconference.

Discussion During the 11/17/21 Teleconference: No discussion occurred

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
  - All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
  - FDA will make a final determination regarding the need for REMS during the review of the NDA.
  - Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components. As per the discussion above, FDA agreed that the results of the hepatic impairment study would be submitted on February 18, 2022. FDA also agreed that Mirati can submit draft reports of 28-day rat GLP toxicity studies evaluating an impurity and GLP hERG study evaluating two metabolites within the planned December 2021 NDA submission provided that final reports and SEND datasets will be submitted in January 2022, along with a summary of changes from the draft reports.

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  NDA NUMBER: LATE COMPONENT - NONCLINICAL

In addition, we refer to the CMC/multidiscipline meeting that was scheduled for August 31, 2021 and later canceled. We refer you to the preliminary comments issued on August 24, 2021.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for

new active ingredients (which includes new salts and new fixed combinations), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and

DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

[4] https://www.fda.gov/media/84223/download
[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[7]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[8]

[6] https://www.fda.gov/media/85061/download
[7] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[8] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

ISSUES REQUIRING FURTHER DISCUSSION
Please refer to the meeting minutes.

ACTION ITEMS
Please refer to the meeting minutes.

ATTACHMENTS AND HANDOUTS
20211116 Response to MRTX849 Preliminary Type B Pre-NDA Meeting FDA Comments (1).pdf

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/s/

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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 138735
Request Receipt Date	April 30, 2021
Product	MRTX849
Indication	Treatment of patients with advanced or metastatic NSCLC with KRAS (p.G12C) mutation (b) (4)
Drug Class/Mechanism of Action	MRTX849 is a small molecule inhibitor of KRAS G12C mutant variant.
Sponsor	Mirati Therapeutics, Inc.
ODE/Division	Office of Oncologic Diseases/Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	June 29, 2021

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

MRTX849 is indicated for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS (p.G12C) mutation (b) (4).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page} Katie Chon, PharmD
Team Leader Signature: {See appended electronic signature page} Erin Larkins, MD
Division Director Signature: {See appended electronic signature page} Harpreet Singh, MD

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Drug Description
MRTX849 is a small molecule inhibitor that binds irreversibly to the KRAS p.G12C cysteine residue, thereby locking the kinase receptor in an inactive conformation.

Disease Background: KRAS p.G12C mutated non-small cell lung cancer
Approximately 13% of patients with metastatic NSCLC harbor a Kirsten rat sarcoma proto-oncogene (KRAS) p.G12C mutation. This mutation leads to persistent downstream signaling from KRAS to pathways promoting cell growth and division including the RAF-MEK-ERK pathway. KRAS mutations are most commonly found in patients with a smoking history, a distinction from other mutations found in NSCLC patients such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (Canon 2019). Other unique features of KRAS-mutated NSCLC are an increased programmed death-ligand1 (PD-L1) expression, high tumor mutational burden (TMB), and responsiveness to immunotherapy (Karatrasoglou 2020; Jeanson 2019). The median overall survival of KRAS p.G12C NSCLC patients treated with immunotherapy has improved to 21-28 months from 10-20 months with chemotherapy alone (Herbst 2019; Gadgeel 2019).

The drug's relation to existing therapy(ies)
See #9 below.

Relevant regulatory history
MRTX849 is not approved in the US for any indication.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Mirati considers overall response rate (ORR), as assessed by a blinded, independent central review according to RECIST v1.1, to be a clinically meaningful, primary endpoint supporting the BTDR. Duration of response (DOR), progression free survival (PFS) and overall survival (OS) are secondary endpoints.

In a confirmatory, randomized trial comparing MRTX849 with docetaxel in patients with KRAS p.G12C-mutated NSCLC previously treated [redacted] (b) (4), Mirati plans to assess progression-free survival and overall survival as co-primary endpoints.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Endpoints accepted by the Division as clinically significant outcome measures for patients with metastatic NSCLC and considered adequate to support traditional approval include an improvement in OS or a large, clinically meaningful improvement in PFS. ORR of large magnitude and long duration is considered to be an

endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with NSCLC (Blumenthal 2015).

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

NONE

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

There are currently no therapies specifically targeting KRAS mutations in NSCLC granted regular approval by the FDA. Sotorasib was recently granted accelerated approval for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior therapy (see #10 below). Patients with KRAS p.G12C have historically been treated with standard therapies approved for NSCLC that does not harbor a targetable mutation (such as EGFR, ALK). First-line standard therapies include immunotherapy alone or in combination with platinum-based chemotherapy. The vast majority of KRAS p.G12C patients will progress on these therapies. After platinum-based chemotherapy and immunotherapy, treatment options are limited to single agent chemotherapy or docetaxel with ramucirumab. The latter combination is toxic and rarely used clinically, while docetaxel monotherapy has a dismal ORR of approximately 5-10%. The following table summarizes available therapies for NSCLC following platinum-based chemotherapy and anti-PD-(L)1 antibody therapy.

Table 1. Available therapies for NSCLC following treatment with platinum-based chemotherapy and anti-PD-(L)1 antibody

Regimen	Intended population	Approval	n	ORR (95% Confidence Interval [CI])
Docetaxel	NSCLC after platinum therapy failure	Regular Primary endpoint: OS[1]	104 (TAX317)	5.5% (1.1, 15.1)
			373 (TAX320)	5.7% (2.3, 11.3)
Docetaxel +Ramucirumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS[2]	628	23% (20, 26)
Pemetrexed	NSCLC (excluding squamous cell histology)	Regular Primary endpoint: OS[3]	283	8.5% (5.2, 11.7)

Median DOR not reported; docetaxel TAX317 median PFS (12.3 vs 7 weeks); docetaxel TAX320 median PFS (8.3 vs 7.6 weeks); docetaxel+ramucirumab median PFS (4.5 vs 3 months); pemetrexed median PFS (2.9 vs 2.9 months)

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Sotorasib (AMG 510) is small molecule inhibitor that binds irreversibly to the KRAS pG12C cysteine residue. Sotorasib receive BTDR on December 7, 2020, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation, as determined by an FDA-approved test, following at least one prior systemic therapy. BTDR was granted based on data reported for 123 patients with ORR of 37% (95% CI 29, 47) and median DOR of 8.4 months. Sotorasib was granted accelerated approval on May 28, 2021, for the same indication as its BTD based on data from clinical study CodeBreaK 100 demonstrating an overall response rate (ORR) of 36% (95% CI 28, 45), a median duration of response of 10.0 months (range: 1.3+, 11.1) and 58% of patients with a duration of response ≥6 months.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 2: Clinical Trial Supporting the BTDR

Study ID	Trial Design	Treatment Group	Patient Group	Results to support BTDR
849-001	Single arm study with two phases: Dose escalation and multicohort dose expansion	MRTX849 600 mg BID	Locally advanced or metastatic NSCLC with KRAS p.G12C mutation previously treated with platinum-based chemotherpy and anti-PD-(L)1 therapy Phase 1/1b plus single-arm Phase 2 (Cohort A) N=45	ORR 42% (95% CI: 28, 58) (investigator assessed; data cutoff March 19, 2021) DoR, median (mos): 5.0 95% CI (mos): (4.01, NE) % DoR ≥6 months: 37%

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

  Study 849-001 is an ongoing dose escalation and multicohort dose expansion study of MRTX849 in patients with advanced solid malignancies with KRAS G12C mutations, including NSCLC. .Patients with active brain metastases were excluded unless patients were neurologically stable for at least 2 weeks prior to enrollment without the use of corticosteroids or are on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

  Results supporting the BTDR are shown in Table 2. The reported ORR of 42% in a refractory KRAS G12C population represents an improvement over available therapies that have ORRs ranging from 6-23%.

  The BTDR references safety data from 202 patients with solid tumors treated with MRTX849 600 mg BID as a single agent reported in the most recent version of the Investigator's Brochure. The most frequent (>20%) treatment emergent adverse events were nausea (59%), diarrhea (52%), vomiting (42%), and fatigue (38%). The most frequent serious adverse advents (occurring in >2 patients) were nausea and vomiting (1.5% each). Among 47 patients with previously treated KRAS G12C-mutated NSCLC treated with MRTX649 600 mg BID, the most frequent (>5%) Grade ≥3 TEAEs were dyspnea (17%), anemia (15%), hypoxia (15%), hyponatremia (13%), lung infection (11%), lipase increased (9%), pericardial effusion (9%), fatigue (6%) and pneumonitis (6%).

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

The ORR and DoR observed in Study 849-001 demonstrate an improvement over currently available therapy for patients with KRAS G12C mutant NSCLC [redacted (b) (4)]. ORR and DoR are accepted endpoints in NSCLC as being predictive of clinical benefit and have been used to support accelerated approvals.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division met with Mirati in July 2020 to discuss the design of their confirmatory trial comparing MRTX849 versus docetaxel in patients with KRAS G12C whose disease has progressed on or after platinum-based chemotherapy and anti-PD-(L)1 therapy. FDA anticipates submission of a meeting request to discuss top-line results from Study 849-001 to potentially support a marketing application seeking accelerated approval when data is available for a larger number of patients with adequate duration of follow-up past onset of response.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Blumenthal GM, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol. 2015 Mar 20;33(9):1008-14.
2. Canon, J., Rex, K., Saiki, A.Y. et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 575, 217–223 (2019).
3. Herbst RS, Lopes G, Kowalski DM, et al. Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in KEYNOTE-042. ESMO Immuno-Oncology Congress 2019.
4. Gadgeel, S. et al. KRAS mutational status and efficacy in KEYNOTE-189: Pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. ESMO Immuno-Oncology Congress 2019.
5. Karatrasoglou, E.A., Chatziandreou, I., Sakellariou, S. et al. Association between PD-L1 expression and driver gene mutations in non-small cell lung cancer patients: correlation with clinical data. Virchows Arch 477, 207–217 (2020).
6. Jeanson A, et al. Efficacy of Immune Checkpoint Inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2019 Jun;14(6):1095-1101.
7. Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel compared with docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non–small cell lung cancer: The SELECT-1 randomized clinical trial. JAMA. 2017;317(18):1844–1853.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page} Katie Chon, PharmD
Team Leader Signature: {See appended electronic signature page} Erin Larkins, MD
Division Director Signature: {See appended electronic signature page} Harpreet Singh, MD

Revised 10/13/20 /M. Raggio

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