1 Clinical Study Protocol

Protocol Title:	**A Phase 1/2, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity of BBT-176 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) who Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI) Agent**
Short Title:	**Phase 1/2 Study of BBT-176 in Advanced NSCLC with Progression After EGFR TKI Treatment**
Protocol Number:	**BBT176-ONC-001**
Version Number and Date:	**V5.0/ 26 Jul 2022**
Drug Product:	**BBT-176**
IND No.:	**146802**
Study Phase:	**1/2**
Sponsor:	[redacted]

Good Clinical Practices (GCP) Statement

This study is to be performed in full compliance with the protocol, GCP, and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

2 TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference for Harmonisation (ICH) GCP and the following United States (US) Code of Federal Regulations (CFR) applicable to clinical studies: 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312.

The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND), Sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

Investigators and clinical trial staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Patients Protection and ICH GCP Training.

The protocol, informed consent form (ICF)(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

3 PROTOCOL SUMMARY

3.1 Synopsis

Name of Study Drug: BBT-176	**Protocol Number:** BBT176-ONC-001

Title of Study:
A Phase 1/2, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity of BBT-176 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) who Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI) Agent

Study Description:
This Phase 1/2 study will be conducted in 2 parts:
[redacted]

Study Objective(s):
Part 1.
Primary Objectives:
- To investigate the safety and tolerability of BBT-176 when given orally to patients with locally advanced or metastatic NSCLC with *EGFR* mutation
- To determine the MTD and/or RP2D of BBT-176 (RP2D may be different for selected mutant types)

Secondary Objectives:
- To characterize the pharmacokinetics (PK) of BBT-176 after a single oral dose and at steady state after multiple oral doses
- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of the Objective Response Rate (ORR) using RECIST version 1.1

Exploratory Objectives:
- To investigate the Duration of Response (DoR) and the Progression-Free Survival (PFS) using RECIST version 1.1
- To investigate the relationship between the anti-tumor activity and blood-borne biomarkers (i.e., circulating tumor DNA [ctDNA])

Part 2.
Primary Objective:
- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of ORR using RECIST version 1.1

Secondary Objectives:
- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of DoR and PFS using RECIST version 1.1
- To evaluate the safety and tolerability of BBT-176 at the RP2D
- To characterize the PK of BBT-176 after a single oral dose and at steady state after multiple oral doses

Exploratory Objective:
- To investigate the relationship between the anti-tumor activity and blood-borne biomarkers (i.e., ctDNA)

Endpoints for Evaluation:

Part 1:
Primary:
- Safety and tolerability (Incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs))

Secondary:
- PK parameters (half-life [T1/2], peak concentration [C_{max}], time to peak concentration [T_{max}], area under the concentration-time curve [AUC])
- ORR per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1)

Exploratory:
- DoR and PFS per RECIST version 1.1
- Pharmacodynamic biomarker (ctDNA)

Part 2:
Primary:
- ORR per RECIST version 1.1

Secondary:
- DoR and PFS per RECIST version 1.1
- Safety and tolerability (Incidence of adverse events)
- Plasma BBT-176 concentrations at steady state

Exploratory:
- Pharmacodynamic biomarker (ctDNA)

Number of Patients to be Enrolled:

[redacted]

Part 1.

- [redacted]
- [redacted]

Part 2.

- [redacted]

Study Design:

This is a Phase 1/2, open-label, multi-center, multiple-dose, dose-escalation and enrichment study of BBT-176 designed in 2 parts.

Part 1. Dose Escalation Phase 1 Study

[redacted]

At the discretion of the [redacted]

Part 2. Enrichment Phase 2 Study

[redacted]

[redacted]

Safety Monitoring:

The study will be monitored by a Safety Monitoring Committee (SMC), comprised of the Principal Investigator for each site, the CRO Medical Monitor, and a Sponsor representative(s) or designee. During the trial, all serious AEs (SAEs) and potential DLTs, as well as any PK results, will be sent to the SMC on a continual basis. The SMC may choose more conservative dosing decisions or stopping rules for the dose-escalation or dose-expansion cohorts.

[redacted]

[redacted] then SMC will convene and review; will recommend the Sponsor to continue or discontinue each of these cohorts.

[redacted] then SMC will convene and review; will recommend to the Sponsor, RP2D for further evaluation in Part 2.

[redacted]

In Part 2 [redacted], the SMC will continually review the safety of [redacted]

Study Periods:

- Screening: [redacted]
- Treatment duration: Patients should continue on treatment with BBT-176 until RECIST v1.1 defined progression, unacceptable toxicities, or until treatment discontinuation criteria (Section 9) are met.
- Safety follow-up: [redacted] after the last administration of study drug or immediately before initiation of any other cancer therapies.

Inclusion/Exclusion Criteria:

Key Inclusion Criteria:

- Provision of signed and dated, written informed consent before any study specific procedures, sampling and analyses
- Histological or cytological confirmation of advanced and/or metastatic stage IIIB/IV NSCLC
- Radiological documentation of disease progression while on a previous continuous (at least 30 days) treatment with an EGFR TKI monotherapy (including, but not limited to, osimertinib, afatinib, dacomitinib, gefitinib, or erlotinib)
- Patients must fulfill all of the following:
  - [redacted]

- **For [redacted]:** [redacted]

Key Exclusion Criteria:

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

- Treatment with any of the following:
  - An EGFR TKI, including but not limited to osimertinib, afatinib, dacomitinib, gefitinib, or erlotinib within 8 days of the first dose of study treatment.
  - Small molecule targeted inhibitor other than EGFR inhibitor class, or cytotoxic chemotherapy within 14 days; biologic anti-cancer medicine (cytokines or antibodies, etc.) within 28 days (before the initiation of BBT-176 treatment) for the systemic treatment of advanced NSCLC
  - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment
  - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment
  - Patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 6 weeks of the first dose of study treatment
- Any unresolved toxicities from prior therapy greater than NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 neuropathy related to prior platinum-therapy
- [redacted]

Investigational Product:

BBT-176 (20 mg, 40 mg, 100 mg) oral capsules

Mode of Administration:

BBT-176 will be administered [redacted]

Comparative Drug(s):

None

Statistical Methods:

Number of Patients

Part 1 – [redacted]

Part 1 of the study will include approximately up to [redacted] with locally advanced or metastatic NSCLC with *EGFR* mutation. Additional patients may be required, depending on the number of cohorts and the number of evaluable patients needed.

Part 2 – [redacted]

An enrichment phase [redacted] selected mutant types will be enrolled and dosed at the RP2D. Given no clinical efficacy had been studied and reported in this patient group, there will be no statistical hypothesis assumed in regard to efficacy. Descriptive statistics will be applied to summarize efficacy.

Statistical Considerations

[redacted]

Efficacy:

[redacted]

[redacted] according to the founder mutation, i.e., exon 19 deletion or L858R, will be analyzed as subgroups.

Pharmacokinetics:

[redacted]

Pharmacodynamics:

Descriptive statistics will be provided for pharmacodynamic parameters whenever applicable. Exploratory analysis of the relationship between pharmacodynamic measurements and PK, efficacy (including biomarker), and safety profiles in patients may be performed.

Safety:

The number and percentage of patients with AEs by system organ class and preferred term will be summarized for each dose level and overall in Part 1, and by cohort and overall in Part 2. Summary statistics will also be provided for laboratory parameters, vital signs, and other safety parameters.

3.2 Schema of Part 1 and Part 2

Figure 1. Schema of Part 1

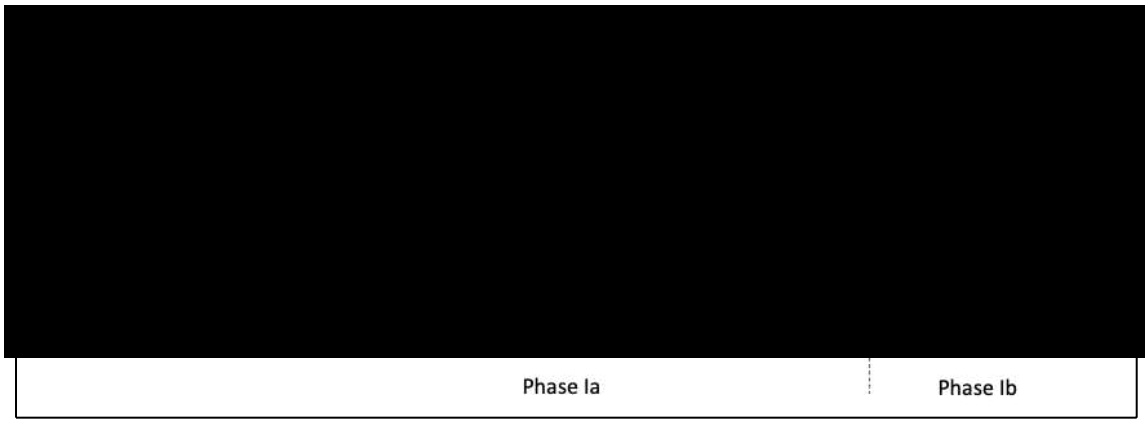


Figure 2. Schema of Part 2

3.3 Schedule of Activities (SoA)

Part 1 (Dose-Escalation and RP2D Exploratory Cohorts, Phase 1)

		Treatment Phase	EOT [a]	Safety F/U [b]

	Screening Phase	Cycle 1	[redacted]		
[redacted]					

a. End of Treatment (EOT) visit: the last day of study treatment administration.
b. Safety F/U visit: 30 days (± 3 days) after the last dose of study treatment or prior to initiation of another systemic anti-cancer therapy, whichever occurs first.
c. The first dose of each cycle is considered Day 1 of each cycle, and cycles will repeat every 21 days unless there is a treatment delay.
d. On Cycle 1, Day 1 before taking dose: confirmation of inclusion/exclusion criteria.
e. Complete physical exams, to include auscultation of the heart for new development of murmur, at Screening, Day 1 of each Cycle, EOT, and Safety F/U visit. If physical or lab findings suggest cardiac damage, echocardiogram or MUGA should be done.

[redacted]

Part 2 (Enrichment, Phase 2)

		Treatment Phase	EOT [a]	

	Screening Phase	Cycle 1	Cycle 2 and Beyond		Safety F/U [b]
[redacted]					

[redacted]

[redacted]

4 INTRODUCTION

4.1 Study Rationale

Lung cancer is one of the most common types of cancer and a leading cause of cancer mortality. In the United States, the majority of lung cancer cases are expected to be non-small cell lung cancer (NSCLC). As a potent molecular driver, the aberration of epidermal growth factor receptor (*EGFR*) is highly correlated with advanced NSCLC. Activating *EGFR* mutations account for 7% to 15% of NSCLC in Caucasian patients and 30% to 50% in East Asian patients (Liu et al 2017, Rotow and Bivona 2017).

The advent of tyrosine kinase inhibitor (TKI) therapy greatly improved outcomes for patients with *EGFR*-mutated NSCLC. However, drug resistance due to T790M mutation severely limits the use of first-generation TKIs, and the most recently approved, third-generation, irreversible TKI osimertinib is rapidly compromised by acquired mutation of C797S. Treatment options for patients whose NSCLC progresses following TKI therapy are limited, contributing to poorer prognosis and high mortality risk. Thus, there is an urgent need for novel EGFR TKIs, particularly ones with efficacy against C797S-triple mutation.

BBT-176 is a competitive TKI that targets selected drug-resistant EGFR mutants, including C797S-triple mutation. In preclinical models, the combination of BBT-176 and cetuximab also showed beneficial synergistic effects on relative tumor volume and survival, as well as on activity of the EGFR signaling pathway.

This is a Phase 1/2 trial to be conducted in 2 parts, the Phase 1 dose-escalation study (Part 1) and the Phase 2 enrichment study (Part 2), to evaluate the maximum tolerated dose (MTD) and to observe tumor response in patients with locally advanced or metastatic NSCLC with *EGFR* mutation.

4.2 Background

Targeted therapy, including EGFR TKIs, developed in the past 2 decades has significantly improved response rates compared with cytotoxic chemotherapy. Activating mutations in the *EGFR* gene cause NSCLC that has been effectively treated by the first-generation EGFR inhibitors, gefitinib and erlotinib (Mok et al 2009, Rosell et al 2012). In EGFR-mutation-positive patients, the response rate was significantly higher with gefitinib treatment (71.2%) than with chemotherapy (47.3%), and progression-free survival (PFS) was significantly longer with gefitinib treatment (9.5 months) than with chemotherapy (6.3 months) (Fukuoka et al 2011). Also, patients in the erlotinib-treated group achieved a higher response rate (58%) compared with the 15% response rate in the chemotherapy group, and PFS of the erlotinib-treated group was significantly longer than that of the chemotherapy-treated group (9.7 months versus 5.2 months, respectively). Molecular analysis showed that the most responder-harboring mutations are the deletion mutation of exon 19 (del19), accounting for 45% of mutations, and the

L858R substitution mutation in exon 21, accounting for 40% to 45% of mutations. These first-generation EGFR TKIs seemed to efficiently control the *EGFR* activating mutation-harboring tumors. However, the toxicity associated with erlotinib or gefitinib was worse than that of chemotherapy, particularly due to the inhibition effect of these TKIs on wild-type EGFR in skin and intestine. More importantly, there was acquired resistance after 9 to 14 months of treatment with the most common resistance mechanism being a point mutation in exon 20 called T790M in EGFR kinase domain (Sequist et al 2015). The secondary mutation, T790M, increases the affinity of Adenosine Triphosphate (ATP) for the binding site, thereby reducing the binding affinity of reversible EGFR TKIs. Third-generation EGFR inhibitors have been developed to overcome T790M resistance through the covalent inhibition of EGFR by binding a cysteine side chain (Cys797). Osimertinib (AZD9291) is the irreversible EGFR TKI approved by the US Food and Drug Administration (FDA) for the treatment of tumors with *EGFR*-activating mutations in the presence of T790M post-TKI resistance and has been significantly effective (Janne et al 2015). Osimertinib is more effective on mutant forms of EGFR (both the activating mutations and T790M) than wild-type EGFR, suggesting the role as a first-line EGFR inhibitor as well. However, despite its critical efficacy, a tertiary mutation (*EGFR* C797S) often appeared in the osimertinib-treated patients, causing acquired resistance and accumulating evidence suggest that both first- and second-line treatment with osimertinib will eventually and ultimately cause C797S triple mutation (Thress et al 2015, Wang et al 2017, and Rangachari et al 2019). Because C797 is the critical covalent binding site of osimertinib, the mutation results in loss of the drug's irreversible inhibition mechanism and, consequently, drug resistance. As such, C797S mutation could be an ideal mechanism to evade the third-generation inhibitor, and a new EGFR inhibitor would be needed to effectively inhibit *EGFR* triple mutants such as del19/T790M/C797S or L858R/T790M/C797S.

BBT-176 is a competitive TKI that targets selected drug-resistant *EGFR* mutants, [redacted]

In vitro pharmacokinetic (PK) studies of BBT-176 have been conducted in the mouse, rat, dog, and monkey. [redacted]

[redacted]

4.3 Risk/Benefit Assessment

4.3.1 Known Potential Risks

In preclinical toxicity studies conducted to date, BBT-176 was negative for in vitro toxicity as assessed by hERG patch clamp, AMES, and micronucleus testing. The animals receiving BBT-176 showed similar class effects as other EGFR TKIs and dose-related toxicological findings including clinical signs, body weights, food consumption, clinical pathology parameters, organ weights, gross pathology, and histopathological examination, with similar toxicity overall compared with brigatinib (for details, refer to the Investigator's Brochure). Therefore, potential risks based on its mechanism of action may be similar to those reported for other EGFR TKIs. For example, brigatinib can cause severe, life-threatening and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis, hypertension, bradycardia, elevated creatine phosphokinase and pancreatic enzymes, hyperglycemia, and embryo-fetal toxicity based on animal reproduction studies, as reported in its Prescribing Information [Prescribing Information of Alunbrig (brigitinib)]. Osimertinib, a kinase inhibitor indicated for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy, can cause ILD/pneumonitis, prolongation of the corrected QT (QTc) interval, cardiomyopathy, and embryo-fetal toxicity based on animal reproduction studies, as reported in its Prescribing Information [Prescribing Information of Tagrisso (osimertinib)].

4.3.2 Known Potential Benefits

BBT-176 is a competitive TKI that has demonstrated in vitro activity and in vivo efficacy against *EGFR* mutants, including those with C797S-triple mutation. BBT-176 in combination with cetuximab demonstrated beneficial synergistic effects that may translate to clinical efficacy. BBT-176 alone or in combination with cetuximab may potentially be of benefit in the treatment of NSCLC with mutations that render other EGFR TKIs ineffective.

4.3.3 Assessment of Potential Risks and Benefits

Overall, the potential benefits of this study are considered to outweigh the potential risks. TKI therapy can be a highly effective treatment for *EGFR*-mutated NSCLC; however, drug resistance greatly limits its utility. Patients whose NSCLC progresses following TKI therapy have limited treatment options and poor prognosis. Evaluation and development of novel EGFR TKIs are needed, particularly ones with efficacy against C797S-triple mutation.

Even if the patient has progressed after TKI therapy, if there is a treatment proven to be effective, it is beneficial for the patient to receive the proven treatment. In particular, if patients with T790M mutation have not yet received osimertinib treatment, it is beneficial for patients to receive osimertinib treatment before participation in this trial. In this case, the Investigator should provide information to the patient so that the patient can receive treatment that has proven effective.

4.3.4 Needs to Explore Alternative Dosing Schedule

[redacted]

5 OBJECTIVES AND ENDPOINTS

5.1 Part 1

Primary Objectives:

- To investigate the safety and tolerability of BBT-176 when given orally to patients with locally advanced or metastatic NSCLC with *EGFR* mutation
- To determine the MTD and/or recommended Phase 2 dose (RP2D) of BBT-176 (RP2D may be different for selected mutant types)

MTD and RP2D:

[redacted]

Secondary Objectives:

- To characterize the PK of BBT-176 after a single oral dose and at steady state after multiple oral doses when given orally
- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of the Objective Response Rate (ORR) using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1

Exploratory Objectives:

- To investigate the Duration of Response (DoR) and the Progression-Free Survival (PFS) using RECIST version 1.1
- To investigate the relationship between the anti-tumor activity and blood-borne biomarkers (i.e., circulating-tumor DNA [ctDNA])

5.2 Part 2

Primary Objective:

- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of ORR using RECIST version 1.1

Secondary Objectives:

- To evaluate the anti-tumor activity of BBT-176 in selected mutant types by evaluation of Duration of Response (DoR) and PFS using RECIST version 1.1
- To evaluate the safety and tolerability of BBT-176 at the RP2D
- To characterize the snapshot PK of BBT-176 at steady state after multiple oral doses

Exploratory Objective:

- To investigate the relationship between the anti-tumor activity and blood-borne biomarkers (i.e., ctDNA)

5.3 Endpoints

5.3.1 Part 1

5.3.1.1 Primary Endpoint

- Safety and tolerability (incidence of adverse events [AEs] and clinical laboratory abnormalities defined as DLTs)

5.3.1.2 Secondary Endpoints

- PK parameters (half-life [$T_{1/2}$], peak concentration [C_{max}], time to peak concentration [T_{max}], area under the concentration-time curve [AUC])
- ORR per RECIST version 1.1

5.3.1.3 Exploratory Endpoints

- DoR and PFS per RECIST version 1.1
- Pharmacodynamic biomarker (ctDNA)

5.3.2 Part 2

5.3.2.1 Primary Endpoint

- ORR per RECIST version 1.1

5.3.2.2 Secondary Endpoints

- DoR and PFS per RECIST version 1.1
- Safety and tolerability (incidence of AEs)
- Plasma BBT-176 concentrations at steady state

5.3.2.3 Exploratory Endpoint

- Pharmacodynamic biomarker (ctDNA)

6 STUDY DESIGN

6.1 Overall Design

[redacted]

6.1.1 Part 1

The primary endpoint in Part 1 is t[redacted]

[redacted]

Intra-patient Dose Escalation:

Intra-patient dose escalation is allowed when the next higher dose level is open to enrollment; A patient has the option to be escalated to the next higher dose level if the patient meets following conditions

1) [redacted]

2) [redacted]

[redacted]onger-term treatment

The Investigator and the Sponsor will continue to monitor safety of BBT-176 for potential cumulative toxicity.

[redacted]

6.1.2 Part 2

In Part 2, the primary endpoint is tumor response [redacted] In Part 2, patients with confirmed *EGFR* mutation types as confirmed in Part 1 will be enrolled to receive BBT-176 to further assess the efficacy, tolerability, and PK of BBT-176. There are no specific stopping criteria for this part of the study and emerging data will be monitored regularly by the SMC.

6.2 Justification for Dose

BBT-176 [redacted] will be the starting dose tested in Part 1 (dose-escalation study).

[redacted]

[redacted]

- Acute gastrointestinal toxicities like nausea, vomiting and diarrhea may be less with BID dosing schedule.
- [redacted]
- [redacted]

[redacted]

6.3 Treatment Duration and End of Study Definition

6.3.1 Treatment Duration

Patients should continue on treatment with BBT-176 until RECIST v1.1 defined progression, unacceptable toxicities, symptomatic progression or until the criteria for treatment discontinuation criteria (Section 9) are met.

A patient is considered to have completed the study when all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA; Section 3.3), have been completed.

6.3.2 End of Study

The trial will be completed when all enrolled patients have discontinued treatment and completed the end-of-study visit and safety follow-up.

7 STUDY POPULATION

7.1 Inclusion Criteria

For inclusion in the study, patients must fulfill all of the following criteria:

1. Provision of signed and dated, written informed consent before any study specific procedures, sampling and analyses
2. Aged at least 18 years
3. Histological or cytological confirmation of advanced and/or metastatic stage IIIB/IV NSCLC
4. Radiological documentation of disease progression while on a previous continuous (at least 30 days) treatment with an EGFR TKI monotherapy (including, but not limited to, osimertinib, afatinib, dacomitinib, gefitinib, or erlotinib). All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study
5. [redacted] World Health Organization (WHO) criteria, after treatment of an EGFR TKI
6. Adequate bone marrow reserve or organ function as demonstrated by all of the following laboratory values:
    - Absolute neutrophil count (ANC) > 1.5×10^9 cells/L (without growth factor support for 2 weeks prior to testing)
    - Platelet count > 75×10^9 cells/L (without transfusion or growth factor support for 1 week prior to testing)
    - Hemoglobin > 9.0 g/dL (without transfusion or growth factor support for 2 weeks prior to testing)
    - Alanine aminotransferase ≤2.5 times the upper limit of normal (ULN)
    - Aspartate aminotransferase ≤2.5 times the ULN
    - Total bilirubin ≤1.5 times the ULN

- Creatinine ≤1.5 times the ULN, creatinine clearance ≥50 mL/min (measured or calculated by Cockcroft-Gault equation). Confirmation of creatinine clearance is required when creatinine is > 1.5 times the ULN

7. [redacted]

8. Patients must have measurable disease per RECIST v1.1 presented
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
10. Females, if of child-bearing potential, should be using adequate contraceptive measures, should not be breastfeeding, and must have a negative pregnancy test result prior to start of dosing, or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at Screening:
    - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
    - Women aged fewer than 50 years will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) levels in the post-menopausal range as defined by the institution
    - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation
11. Male patients should be willing to use barrier contraception (i.e., condoms)

7.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Treatment with any of the following:
    - An EGFR TKI, including but not limited to osimertinib, afatinib, dacomitinib, gefitinib, or erlotinib within 8 days of the first dose of study treatment.
    - Small molecule targeted inhibitor other than EGFR inhibitor class, or cytotoxic chemotherapy within 14 days; biologic anticancer medicine (cytokines or antibodies, etc.) within 28 days (before the initiation of BBT-176 treatment) for the systemic treatment of advanced NSCLC
    - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment
    - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment
    - Patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation within 6 weeks of the first dose of study treatment
    - Patients receiving CYP2C8 or P-gp strong inhibitor (see Appendix 4)
2. Any unresolved toxicities from prior therapy greater than NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0) Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 neuropathy related to prior platinum-therapy
3. Spinal cord compression or brain metastases, unless asymptomatic and stable fulfilling one of following:
    - Not requiring active treatments prior to start of study treatment
    - Requiring stable dosing regimens of low-dose oral corticosteroid (up to 20 mg prednisone/day or equivalent) for at least 4 weeks prior to the first dose of study treatment
4. Even if the patient has progressed after EGFR TKI therapy, if there is a treatment proven to be effective, the patient should receive the treatment first. This includes cases where documented evidence of *MET* amplification, *HER2* mutation, or SCLC transformation exists and treatments or clinical trials that have been proven for the corresponding mutations are available.
5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses that in the Investigator's opinion makes it

undesirable for the patient to participate in the trial or would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). Screening for chronic conditions is not required

6. Any of the following cardiac criteria:
    - Mean resting QTc interval (corrected by Fridericia's formula [QTcF]) > 470 msec obtained from average value of 3 electrocardiograms (ECGs), using the screening clinic ECG machine derived QTc value
    - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block, second degree heart block, or PR interval of >250 msec)
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as heart failure (ejection fraction < 50%; for details refer to Section 10.2.3.3), hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death before the age of 40 years in first-degree relatives, or any concomitant medication known to prolong the QT interval
7. Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD
8. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the study treatment, or previous significant bowel resection that would preclude adequate absorption of BBT-176
9. Involvement in the planning and conduct of the study
10. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements
11. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, carcinoma in situ of cervix, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured
12. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds
13. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dose

7.3 Tumor and Mutation Assessment for Eligibility

The RECIST assessment by the Investigator/local radiologist will be the basis for eligibility, continuation, or discontinuation of the trial in an individual patient. The independent central RECIST v1.1 review will be conducted.

EGFR mutational status for eligibility will be assessed in medical history, ctDNA, and/or tumor tissue from each patient.

For Part 1, [redacted]

7.4 Screen Failures

Screen failures are defined as participants who consent to participate but are not subsequently enrolled in the study. Minimal screening failure information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Potential study participants may have inclusionary laboratory one single time repeated during the screening period for inclusion. Patients recorded as a screen failure may be rescreened once per investigator's discretion.

7.5 Definition of Evaluable Patient (For Part 1 Dose Escalation Cohorts)

An evaluable patient is defined as a patient who has completed minimum safety evaluation requirements during the first 21 days or has experienced a DLT during the first 21 days.

[redacted]

During Part 1 dose escalation cohorts, in the case that patients in the cohort are not evaluable, additional patients will be enrolled in the cohort.

Patients who are not evaluable might continue trial treatment upon agreement between Investigator and Sponsor, however the patient will not be considered for the evaluation of MTD.

8 STUDY TREATMENT AND DOSE MODIFICATIONS

8.1 Study Treatment(s) Administration

8.1.1 Study Treatment Description

BBT-176 is a competitive TKI that targets selected drug-resistant *EGFR* mutants, including C797S-triple mutation.

8.1.2 Method of Assigning Patients to Treatment Groups

For Part 1, the eligible patients will be assigned to the dose escalation cohorts first, and to exploratory cohorts if there are no available dose escalation cohorts.

An Interactive Web Response System (IWRS) system will be deployed to manage the supply of BBT-176 capsules to sites and to manage the dispensing of BBT-176 to patients.

The treatment medication assignment will be managed through an IWRS system. In addition, patient's screening, dose assignment, all drug dispensation visits, and EOT visit will be documented in the IWRS system.

Screening and treatment slots are assigned according to the cohort management plan. After the Sponsor (or designated CRO) has been notified by a site about a potential patient, the slot will be reserved to this site for a maximum of 7 calendar days. If the informed consent form (ICF) has not been signed by the potential patient within this time window, the slot will be opened up again for all recruiting sites.

Patients who meet the eligibility criteria and who have given their written informed consent will be entered into the study.

Before entering patients at the next dose level, it will be ensured that all patients at an ongoing cohort have completed the first cycle. Prior to inclusion of a new patient, the Investigator should confirm the respective dose with the Sponsor (or designated CRO).

8.1.3 Dosing and Administration

8.1.3.1 Dosing and Meal Timing

There is no meal restriction on BBT-176 dosing. Patients will take BBT-176 at home at about the same time every day, except on days with scheduled study visits including pre-dose PK sampling, patients should not take their dose of study medication at home in order to complete pre-dose PK plasma collection.

8.1.3.2 Starting Dose and Dose Levels

BBT-176 will be administered orally once daily at a starting dose of 20 mg in Cohort 1. The starting dose justification is described in Section 6.2.

The dose-escalation scheme proposes [redacted] as shown in Table 1.

[redacted]

In case 160 mg BID is assessed to be intolerable by the Safety Monitoring Committee, then 120 mg BID may be explored further. Dosage and frequency for Dose level ≥2 may be altered based on the PK, pharmacodynamics, and safety data obtained from previous dose level.

8.1.3.3 Dose Escalation

Bayesian Model-based Method for dose escalation:

Bayesian model-based method will be used for the next dose recommendation for dose escalation. Dose-escalation of BBT-176 to determine the MTD will be guided by the mCRM using a BLRM following dose [redacted]

Prior Distribution Specification

The prior distribution will be calculated based on:

1. Probability of DLT at [redacted] mg (starting dose): 0.05

2. Estimate of MTD: [redacted]

In the 28-days GLP toxicology study, t[redacted] herefore, patients [redacted] are not expected to show DLT. Based on these, [redacted]

The [redacted] on these, [redacted]

[redacted]

The acceptable dose range is on a continuous scale between the minimum and maximum doses. The upper limit of the acceptable range is the largest dose whose probability of overdosing is less than the EWOC threshold. The lower limit of the acceptable range is the dose whose DLT rate is equal to the lower limit of the targeted toxicity interval.

When the acceptable dose range of the next cohort is recommended by the BLRM, the SMC will decide the next dose within the acceptable dose range or a lower dose than the lower limit. The SMC will consider the following for the dose decision:

- [redacted]

Intermediate or lower dose levels, as long as they fulfil the EWOC criterion, may be recommended by the SMC and investigated if agreed upon between Investigator and Sponsor.

[redacted] will be applied to guide [redacted] The [redacted]

[redacted]

8.1.3.4 RP2D Exploration

At the discretion of the Sponsor, once the RP2D has been provisionally established, [redacted] additional patients with molecularly defined biomarker may be enrolled and treated at that dose in order to further characterize safety, tolerability, PK, and efficacy, and to confirm its selection as the optimal dose to evaluate in Phase 2. RP2D exploration may be conducted in more than one cohort according to mutant types.

The [redacted]

8.1.3.5 [redacted]

[redacted]

8.1.3.6 Dose Reduction Criteria

In Part 1, no dose reduction is permitted in Cycle 1 without the Sponsor approval. If a patient in Part 1 is confirmed to have experienced a DLT in Cycle 1, then the Investigator, with the Sponsor approval, may do either of the following:

- Continue treating the patient at the next lower dose level evaluated, if the Investigator expects clinical benefit from further treatment, the toxicity is manageable, and the Investigator and the Sponsor's medical monitor (or designee) agree. A patient who receives a modified dose will be evaluated for safety at that dose level, but will not be counted towards the number of patients with DLTs at that dose level.
- Discontinue the patient from the treatment and the study.

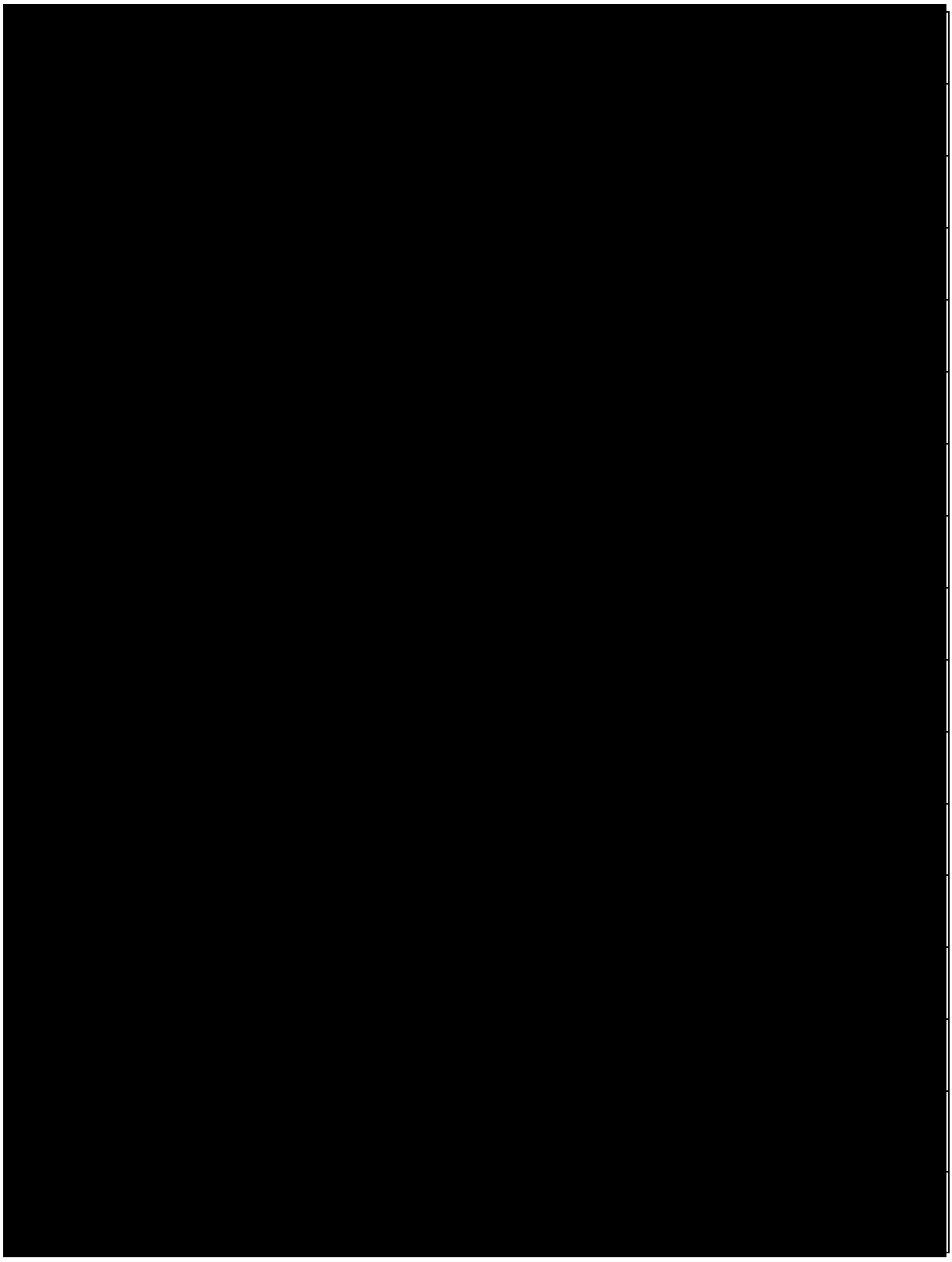
Treatment with BBT-176 should be held until the toxicity resolves to ≤Grade 2. Dosing may then be resumed at either the same dose or the next lower dose level evaluated, per Investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same

toxicity, the dose should be reduced following treatment hold and resolution of the event. If the patient continues to experience toxicity, a second dose reduction to a previously evaluated lower dose is permitted. Only two dose-reduction steps are allowed. If a patient continues to experience toxicity after two dose-reduction steps, or if dosing with BBT-176 is interrupted for >14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed upon between the Investigator and the Sponsor.

During Part 1, after Cycle 1, up to two dose reduction steps are allowed for each patient, if CTCAE Grade 3 or 4 toxicities are observed. The dose may be held or continued at the next lower dose level as described below.

For the RP2D exploratory cohort, the Investigators will have discretion to adjust dose in individual patients according to tolerability and safety from Cycle 1. Two dose reductions steps are allowed. If a patient continues to experience toxicity after two dose reduction steps, or if dosing with BBT-176 is interrupted for >14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed upon between the Investigator and the Sponsor. The dose may be increased, if the sponsor agrees, not exceeding MTD, when such concerns are resolved or mitigated. The Investigator may consult to the Sponsor about dose adjustment. Below table is an example. In case of not-specified adverse events, the Investigator and the Sponsor will discuss further and determined the adjusted dose according to available scientific literatures.

Table 2. Recommended Dose Adjustment Scheme



[redacted]

If a patient at the RP2D was required to reduce their dose level due to a non-drug-related toxicity, and the toxicity subsequently resolved, then the dose may be re-escalated back to the recommended dose, if tolerated.

8.2 Preparation, Handling, Storage, and Accountability

8.2.1 Acquisition and Accountability

The Investigator will maintain accurate records of the receipt of all study medications. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the site. The Investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

8.2.2 Formulation, Appearance, Packaging, and Labeling

BBT-176 is [redacted] The formulated BBT-176 contains citric acid and pharmaceutically acceptable excipients. For [redacted]

8.2.3 Product Storage and Stability

Bottles containing BBT-176 should be stored at temperatures of 15°C to 30°C (59°F to 86°F), protected from high humidity and direct sunlight. The cap on the bottle should be tightly closed after each use and out of the reach of children.

8.2.4 Preparation

No preparation is required for BBT-176.

8.3 Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable to this non-randomized, open-label trial.

8.4 Study Treatment Compliance

Adherence to administration of study treatment will be assessed by the amount of study treatment distributed versus the amount returned.

The appropriate number of capsules for 3 weeks treatment will be provided to patients to be self-administered at home. Patients will be asked to bring the remaining trial medication at the end of each cycle to the Investigator site for a compliance check. Remaining capsules will be counted by Investigator/site staff and recorded. Discrepancies between the number of capsules remaining and the calculated number of capsules the patients should have taken must be documented and explained. If the patient is eligible for further treatment, a new bottle of study drug will be dispensed.

In case a patient feels uncomfortable from the number of capsules, divided oral intake within 20 minutes is allowed.

Patient diary will also be assessed as a supplementary method for treatment compliance check.

In case a patient is unable to comply to the protocol-defined procedures due to public health policy, e.g., COVID-19 pandemic quarantine measures, the Investigator may delay physical examinations and laboratory examinations if the sponsor agrees. The Investigator should try every effort to communicate directly with the patient for safety follow-up, e.g., by telephone call or video conference. Such communications must be documented in eCRF.

8.5 Prior and Concomitant Therapy

Prior medication will be recorded as part of the past medical history.

Concomitant therapy is defined as any medicinal product, prescribed or over-the-counter, taken by a patient other than the study drug. Use of concomitant medications will be recorded and reported. The Investigator will have discretion to prescribe medications which are recommended by public treatment guidelines to prevent or mitigate adverse events in cancer patients, e.g., nausea, vomiting, or diarrhea.

The Investigator will be responsible for preventive vaccination of the subjects according to the available public health policy of the jurisdiction where this clinical trial is being conducted. The Investigator may discuss with the Sponsor on individual decisions.

8.5.1 Emergency Procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude drug-induced ILD. Study drugs should be interrupted pending investigation of these symptoms. If drug-induced ILD is diagnosed, appropriate treatment should be instituted as necessary.

8.5.2 Restrictions

- Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.
- Palliative radiotherapy may be given as described above.
- Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate for decreased appetite), or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.
- [redacted]

9 STUDY TREATMENT DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 Discontinuation of Trial

This study may be temporarily suspended or prematurely terminated by the Sponsor if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination by the Sponsor will be provided to investigators or the Sponsor, respectively; study participants; the Institutional Review Board (IRB); and regulatory authorities. Study participants will be contacted, as applicable, and be informed of any changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Failure to meet enrollment goals overall or at a particular trial site

The study may resume once concerns are addressed to the satisfaction of the Sponsor, IRB, and/or regulatory authorities.

9.2 Participant Discontinuation/Withdrawal from the Study

Patients are free to withdraw from participation in the study at any time upon request. A patient may be withdrawn from the study by the Investigator or designee and not be allowed to continue the study if any of the following occur:

- Withdrawal of consent by the patient
- Withdrawal of patient at the discretion of the Investigator or designee if concurrent illnesses occur that may invalidate the study data or are considered to increase the risk from the study participation
- Discovery that the patient has entered the study in violation of the inclusion/exclusion criteria stated in the protocol
- Significant critical protocol violation occurs during the study
- Pregnancy

The reason for discontinuation or withdrawal from the study will be recorded. Patients who sign the ICF and are discontinued or withdrawn from the study should visit the clinic for EOT procedures shown in the SoA (Section 3.3). Samples and data collected from patients up to the point of discontinuation/withdrawal may still be included in the analyses.

9.3 Lost to Follow-Up

A patient will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff. If a patient fails to return to the clinic for a required study visit, the site will attempt to contact the patient and reschedule the missed visit and ascertain if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact. These contact attempts should be documented in the participant's medical record or study file.

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 Efficacy Assessments

The following efficacy parameters will be measured:

- Tumor response according to RECIST, version 1.1: ORR, DoR, PFS (at Screening and every 6 weeks from Cycle 1 Day 1 until progression
- Biomarker analysis: ctDNA (at Screening and every 2 cycles until progression)

10.1.1 Tumor Assessment (RECIST v1.1)

Tumor assessment (RECIST version 1.1) will be performed at Screening and every 6 weeks from Cycle 1 Day 1 until progression of disease, EOT, or until the patient commences further anti-cancer treatment, whichever comes first.

- Imaging may be performed within 7 days before the scheduled visit.
- In the event of a delay or discontinuation of study drug, tumor assessment should continue to follow the original schedule.

The Investigator will choose the anatomical extent and the modality of imaging study, while brain MRI is mandatory at screening. The assessment by the Investigator/local radiologist will be the basis for eligibility, continuation, or discontinuation of the trial in an individual patient.

[redacted]

10.1.2 Circulating Tumor DNA Assessment

[redacted]

10.1.3 Tumor Biopsy

[redacted]

10.1.3.1 Archival Tumor Blocks Taken Before the Study

[redacted]

10.2 Safety Assessments

10.2.1 Maximum Tolerated Dose

[redacted]

10.2.2 Dose Limiting Toxicity

A [redacted]

last day of Cycle 1 (21 days after start of multiple dosing) in dose-escalation cohorts and that

A DLT excludes:

1.

The incidence and type of AE fulfilling the above DLT criteria from Cycle 2 within each cohort/dose level and beyond will be taken into account by the SMC in determining dose-escalation steps and will be considered when selecting the RP2D by the Sponsor.

Any DLT must be immediately (within 24 hours of first knowledge) reported to the Sponsor.

10.2.3 Adverse Events and Other Safety Assessments

For details of AE assessment refer to Section 10.6.

10.2.3.1 Laboratory Tests

Laboratory tests includes:

Complete blood count with differential, platelet count and ANC

Plasma: total protein, albumin, creatinine, blood urea nitrogen (BUN), uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), glucose, calcium, phosphorus, chloride, sodium, potassium, magnesium, serum amylase, serum lipase, and coagulation tests (prothrombin time [PT] or international normalized ratio [INR], activated partial thromboplastin time [aPTT]).

Serology (at Screening): hepatitis B surface antigen (HBsAg), Anti-hepatitis C virus (HCV), HIV test

Urine: glucose, protein, blood

10.2.3.2 Electrocardiogram

Twelve-lead ECG will be performed at the visit indicated in the SoA (Section 3.3). The timing and number of ECGs may be altered depending on the emerging PK and safety profile.

Twelve-lead ECGs will be obtained after the patient has been resting supine or semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same physical position. Screening, Day 1 of each Cycle, EOT, and Safety F/U visit. Serial ECGs will be conducted on Cycle 1, Day 1 pre-dose and at 2 (±10 min), 4 (±15 min), and 6 (±15 min) h post-dose, on Day 2 prior to discharge. When ECGs are scheduled at the same time as blood draws, the ECGs will be obtained prior to and as close to the scheduled blood draw as possible. For screening and each time point of Cycle 1, ECG recording should be repeated 3 times with an interval of about 5minutes. Single ECG recording will be taken from Cycle 2. A standardized ECG machine should be used, and the patient should be examined using the same machine throughout the study if possible.

From version 5.0. ECG on Day 2 is not applicable.

After ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A copy should be filed in the patient's medical records. If an abnormal ECG finding at Screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, ECG intervals, and an overall evaluation will be recorded.

10.2.3.3 Echocardiogram/Multiple-gated Acquisition (MUGA) Scan

At Screening: only patients with suspect cardiac disease with negative effect on ejection fraction (EF) will be measured during Screening according to local standards at the Investigator's discretion (e.g., echocardiogram or MUGA). Echocardiogram or MUGA scan within 6 months is accepted for screening assessment.

During the study and safety follow-up visit, if physical or lab findings suggest cardiac damage, echocardiogram or MUGA should be done.

10.3 Pharmacokinetics

Venous blood samples will be collected to measure the BBT-176 concentrations in plasma as well as the following PK parameters:

- $T_{1/2}$ (Part 1 only)
- C_{max}
- T_{max}
- AUC (Part 1 only)
- C_{trough} (Part 1 only)

[redacted]

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterization of the plasma concentration-time profiles.

A 10-minute window will be allowed for samples taken at 1 hour; a 20-minute window for samples taken at 2 to 8 hours; and a 1-hour window for samples taken at 12 and 24 hours. In case of divided dosing, blood collection time must be measured from the time of the first divided intake.
Details about blood sample collection, preparation of sample, storage/shipment, and disposal will be provided in the laboratory manual.

10.4 Volume of Blood

The number of samples taken, as well as the volume required for each analysis, may be changed during the study as new data become available. The estimated total volume of blood that will be

drawn from each patient in this study for mandatory samples up to the end of Cycle 2 is approximately [redacted]

Safety laboratory assessments will be performed locally at each site's laboratory by means of their established methods. The number of samples/blood volumes is therefore subject to site-specific change.

10.5 Study Procedures

The first dose of each cycle is considered Day 1 of each cycle, and cycles will repeat every 21 days unless there is a treatment delay. Please refer to 3.3 Schedule of Activities (SoA) for each visit window.

10.5.1 Part 1 (Dose-Escalation and RP2D Exploratory Cohort, Phase 1)

[redacted]

[redacted]

[redacted]

[redacted]

Safety Follow-up

Safety follow-up should be performed 3[redacted] after the last administration of study drug or immediately before initiation of any other cancer therapies.

- Complete physical examination, including measurement of weight, auscultation of the heart for new development of murmur (if physical or lab findings suggest cardiac damage, echocardiogram or MUGA should be done)
- ECOG performance status
- Vital signs
- Laboratory tests
- Serum pregnancy test in female patients of childbearing potential
- 12-lead ECG
- Concomitant medications

- AE assessments

10.5.2 [redacted]

[redacted]

[redacted]

- Complete physical examination, including measurement of weight, auscultation of the heart for new development of murmur (if physical or lab findings suggest cardiac damage, echocardiogram or MUGA should be done)
- ECOG performance status
- Vital signs (including blood pressure, heart rate, respiratory rate, and temperature)
- Laboratory tests: pre-dose
- Serum pregnancy test in female patients of childbearing potential
- 12-lead ECG: pre-dose
- Return BBT-176 and diary review
- BBT-176 and diary distribution
- Whole blood sampling for ctDNA (every 6 weeks from Cycle 1 Day 1, within 7 days from Day 1 of odd number of cycles [Cycles 3, 5, 7, and so on])
- RECIST version 1.1 tumor assessment (every 6 weeks from Cycle 1 Day 1, within 7 days from Day 1 of odd number of cycles [Cycles 3, 5, 7, and so on])
- Concomitant medications
- AE assessments

[redacted]

Safety Follow-up

Safety follow-up should be performed [redacted] after the last administration of study drug or immediately before initiation of any other cancer therapies.

- Complete physical examination, including measurement of weight, auscultation of the heart for new development of murmur (if physical or lab findings suggest cardiac damage, echocardiogram or MUGA should be done)
- ECOG performance status
- Vital signs
- Laboratory tests
- Serum pregnancy test in female patients of childbearing potential
- 12-lead ECG
- Concomitant medications
- AE assessments

10.6 Adverse Events and Serious Adverse Events

10.6.1 Definition of Adverse Events (AE)

The descriptions found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting. In case of AE(s), investigators may perform unscheduled clinical examination(s), intervention(s), etc. for AE management.

10.6.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.6.2.1 Exceptional Events of SAE

Following cases will not be considered as SAEs. These cases will be reported to Sponsor or Syneos Health same as Aes.

- A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- An elective surgery or preplanned procedure to treat a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
- A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.

- Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Hospitalization for an event solely related to disease progression is not considered an SAE.
- If progressive disease occurs and is associated with symptoms the meet the definition of SAE, the term "PD" should not be reported as SAE, however signs and symptoms of PD will be reported as an SAE.

10.6.3 Classification of an Adverse Event

10.6.3.1 Severity of Event

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE scoring.

10.6.3.2 Relationship to Study Treatment

All Aes will have their relationship to study treatment assessed as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

10.6.3.3 Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

10.6.4 Time Period and Frequency for Event Assessment and Follow-up

Assessments for Aes will be conducted on all study visits indicated in the SoA (Section 3.3). The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (for non-serious Aes) after the last day of study participation or until resolution or stabilization (for SAEs). At each study visit, the Investigator will inquire about the occurrence of AE/ SAEs since the last visit.

10.6.5 Adverse Event Reporting

All Aes occurring while on study must be documented appropriately regardless of relationship. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of the event. Any medical condition that is present at the time of screening and is highly likely to have been present from before obtaining ICF will not be reported as an AE, but will be reported as part of medical history. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE (worsening of the underlying disease or of other pre-existing

conditions will be recorded as an AE in the eCRF). Changes in vital signs, ECG, physical examination, and lab test result deemed clinically significant by the Investigator will be recorded as AE in the eCRF.

Collection and Reporting of PD:

If progressive disease occurs and is associated with symptoms, the term "PD" should not be reported as an AE, however signs and symptoms of PD will be reported as an AE.

10.6.6 Serious Adverse Event Reporting

Any SAE must be reported to the Sponsor or Syneos Health Safety and Pharmacovigilance within 24 hours of awareness of the event, whether or not considered study treatment-related, and must include an assessment of whether there is a reasonable possibility that the study treatment caused the event.

Email Address: safetyreporting@syneoshealth.com

Fax: +1 877 464-7787

The Investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents.

All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or the patient is stable. Other supporting documentation of the event may be requested by the Sponsor or Sponsor's representative and should be provided as soon as possible.

The Sponsor will be responsible for notifying the Regulatory agencies and all participating Pis of potential serious risks as soon as possible, but in no case later than 15 calendar days after the Sponsor/Investigator determines that the information qualifies for reporting (21 CFR 312.32I(1)). The Sponsor and Sponsor's representative must notify the FDA and all participating PIs of any suspected unexpected fatal or life-threatening adverse reactions as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information (21 CFR 312.32(c)(2)).

10.6.7 Reporting Events to Participants

Not applicable.

10.6.8 Adverse Events of Special Interest

DLT evaluation will occur in Part 1. Please refer to Section 10.2.2 for definition of DLTs.

AEs of special interest (AESI) for the purposes of this study, based on the known safety profiles of EGFR inhibitors, include gastrointestinal (>Grade 2), skin (>Grade 2), pulmonary (≥Grade 2), and/or serious events requiring reporting to the Sponsor as an SAE.

Any laboratory hepatic toxicity meeting Hy’ s law criteria for suspected severe drug induced liver injury, defined as a rise in serum aminotransferases (AST or ALT) of >3 × ULN and total bilirubin ≥2 × ULN, in the absence of any alternative reason (e.g., liver metastasis, liver disease, or concomitant medication), will also be considered an AESI.

Protocol-specified AESI are to be reported in an expedited manner, similar to an SAE, even if they are not an SAE (within 24 hours).

10.6.9 Overdose

Special situations including overdose are not in themselves AEs, but may result in AEs.

An overdose in which signs, symptoms, or abnormalities meet the definition of an AE or SAE must be fully documented and reported consistent with AE and SAE reporting guidelines.

10.6.10 Reporting of Pregnancy

Although not an AE in and of itself, pregnancy as well as its outcome must be documented, as at least one of the study medications in this study is known to have risk of embryo-fetal toxicity.

All female patients who are capable of becoming pregnant will be asked to provide consent to use a highly effective contraception to avoid pregnancy (for female patients a double-barrier method of contraception, for male patients a condom with spermicide) or total abstinence from the time of providing informed consent until 30 days after the last dose of study drug. Use of oral contraceptives is not allowed as a method of birth control.

Reports of pregnancy of a patient or female partner must be reported and recorded on the Sponsor’s or Sponsor approved pregnancy form and must be submitted to Syneos Health Safety & Pharmacovigilance within 24 hours of awareness:

Email Address: safetyreporting@syneoshealth.com

Fax: +1 877 464-7787

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

11.1.1 Part 1

Dose-Escalation: up to 48 patients with locally advanced or metastatic NSCLC with *EGFR*

11.2 Populations for Analysis

[redacted]

11.3 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in the data listings and tabulations. No imputation of values for missing data will be performed.

11.4 General Methodology

[redacted]

11.5 Baseline Comparison

Demographic and baseline characteristics will be summarized by cohort.

11.6 Efficacy Analysis

[redacted]

11.6.1 Objective Response Rate

[redacted]

[redacted]or-evaluable population by cohort, additionally. 80% confidence intervals will be provided.

11.6.2 Progression-Free Survival

[redacted]

11.6.3 Duration of Response

[redacted]

11.7 Safety Analysis

Safety variables to be assessed will include AEs, laboratory test results (hematology, clinical chemistry, and urinalysis), ECG, weight, and vital signs.

Adverse event terms recorded ion the eCRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 23.0 or later. The number and percentage of patients with AEs will be summarized for each dose level and overall according to the system organ class and preferred term. Adverse events (including AESI) will be summarized for overall frequency (number and percentage of patients), worst reported severity, and relationship to study treatment for each preferred term per patient. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

Laboratory variables will be summarized using actual values and changes from baseline to scheduled time points. Laboratory values will also be categorized according to their CTCAE (v5.0) toxicity grade and tabulated by worst on-study toxicity grade. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first BBT-176 dose.

ECG, weight, and vital signs will also be summarized by actual values and changes from baseline to scheduled time points using descriptive statistics. Changes in QTcF will also be evaluated for the proportion of patients with absolute values > 500 msec and change from baseline > 60 msec.

11.8 Pharmacokinetic Analysis

The PK profile of BBT-176 will be analyzed by measurement of area under the plasma concentration-time curve [(AUC_{last}, AUC_{inf}, AUC_{τ})], C_{max}, T_{max}, and $T_{1/2}$. C_{trough} will also be presented. Individual and mean concentration-time curves on linear and semi-logarithmic scales will be provided.

11.9 Pharmacodynamic Analysis

All pharmacodynamics biomarker analyses will be based on the pharmacodynamics population.

No formal statistical analysis of pharmacodynamics endpoints will be performed. Pharmacodynamics data from each assay will be listed by cohort and patient. Summary tables of values (n, mean, median, standard error of the mean, standard deviation) will be created for each pharmacodynamics biomarker. Exploratory analysis of the relationship between pharmacodynamic measurements and PK, efficacy, and safety profiles in patients may be performed.

11.10 Interim Analysis

Interim analysis will be performed, if necessary.

[redacted]

12 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1 Informed Consent Process

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH Good Clinical Practice (GCP). Prior to the beginning of the trial, the Investigator should have the IRB's written approval for the protocol and the written ICF(s) and any other written information to be provided to the participants.

12.2 Consent and Other Informational Documents Provided to Participants

The IRB-approved ICF describing in detail the study treatment, study procedures, potential benefits and risks is to be given to the participant, and written documentation of informed consent is required prior to administering the study treatment.

The ICF contains a statement that consent is freely given, that the patient is aware of the risks of entering the study, and that the patient is free to withdraw from the study at any time. Informed consent must be given by the patient and/or legal representative after the receipt of detailed information on the study.

12.3 Consent Procedures and Documentation

The informed consent process will be initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the patients and their families.

ICFs will be IRB-approved, and the patient will be asked to read and review the document. The Investigator will explain the research study to the patient and answer any questions that may arise. All patients will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients will have the opportunity to discuss the study with their family members or think about it prior to agreeing to participate. The patient will sign the ICF prior to any procedures being done specifically for the study.

The patients may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the Sponsor, and their agents. This confidentiality is extended to cover testing of biological samples

and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Study participant contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

12.5 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 12.6.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to only authorized users via the study's internet web site, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

As part of understanding the PK of the study drug, plasma samples may be used for metabolite identification and profiling evaluation. As part of understanding the efficacy and safety of the study drug, biopsy samples may be used for gene expression and profiling evaluation. Residual plasma and biopsy samples may be stored up to 5 years from study completion. If the residual samples are used, the results will be reported to the regulatory agencies.

12.6 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

12.7 Record Retention

Study records and source documents must be preserved for at least 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational drug, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

12.8 Safety Monitoring Committee

The study will be monitored by an SMC comprised of the PI for each site, the CRO Medical Monitor, and a Sponsor representative(s) or designee. During the trial, all SAEs and potential DLTs, as well as any PK results, will be sent to the SMC on a continual basis. The SMC may choose more conservative dosing decisions or stopping rules for the dose-escalation cohorts. The patients who exercised the option of intra-patient dose escalation will be monitored by the SMC as well. Ad hoc SMC meeting may be convened to discuss potential DLT cases more in depth.

In Part 1 of the trial (dose-escalation cohorts), the SMC will decide the dose of BBT-176 for the next cohort, as well as define the MTD, based on available PK, statistical assistance tool (BLRM or mTPI-2), safety findings. The RP2D may be set lower than the MTD if there are concerns about tolerability or if the analysis of biomarker and pharmacodynamic data suggests a lower dose would be appropriate.

In RP2D exploratory cohort, SMC will make balanced evaluation and recommendation about RP2D based upon safety, PK, efficacy including biomarker data.

When clinical data of at least six patients are available from each of two subgroups of this cohort, then SMC will convene and review; will recommend the Sponsor to continue or discontinue each of these cohorts.

When clinical data of at least twelve patients are available from each of two subgroups , then SMC will convene and review; will recommend to the Sponsor, RP2D for further evaluation in Part 2.

Even after RP2D is determined, the Sponsor may continue to enroll patients into RP2D exploratory cohort up to 30 patients in each cohort.

In Part 2 of the trial (enrichment), the SMC will continually review the safety of BBT-176.

The SMC will assess safety data and operate under the rules of an approved charter that will be written and reviewed at the inception of the SMC. At that time, each data element that the SMC needs to assess will be clearly defined. The SMC will provide its input to the Sponsor and CRO as needed.

Further information describing the SMC scope and procedures will be provided in the SMC Charter.

12.9 Clinical Monitoring

The Sponsor has engaged the services of a CRO, to perform all monitoring functions within this clinical study. CRO monitors will work in accordance with CRO Standard Operating Procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also ensure adherence to the protocol at the study center. They will arrange for the supply of study treatment and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification) including, but not limited to:

a. Patient identification number
b. Patient consent obtained

c. Patient eligibility criteria (inclusion and exclusion criteria)
d. Efficacy variables
e. Medical record of AE

12.10 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and at each stage of data handling. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Sponsor (or designated CRO) is responsible for implementing and maintaining quality assurance (QA) and QC systems with written SOPs. In accordance with the written SOPs, monitors will verify that the clinical trial is conducted, data are generated, and biological specimens are collected, recorded, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practice [GMP]). The Sponsor and monitor will determine the frequency of monitoring visits.

During the study, the Sponsor may conduct audits separately from routine monitoring. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for routine monitoring and/or auditing by the Sponsor, and inspection by local and regulatory authorities.

12.11 Protocol Deviations and GCP Non-Compliance

A protocol deviation is any noncompliance to the clinical trial protocol and non-compliance with ICH/GCP; both will be monitored and reported as per local regulations. The non-compliance may be on the part of the patient, the Investigator, or the study site/CRO staff. Protocol deviations must be documented, and corrective actions have to be developed and implemented promptly.

It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations timely. All deviations must be addressed in study source documents and reported to the monitor and/or Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

For protocol deviations deemed to have no influence on the interpretation of study results, the level and reason of deviation or delay will be accurately described and comprehensively considered by the Investigator, Sponsor, monitor, or statistician.

Protocol waivers are not permitted. Neither CRO nor Sponsor approves of protocol waivers, as per GCP and regulatory guidelines. All major protocol deviations should be listed in the Clinical Study Report.

12.12 Publication and Data Sharing Policy

The data generated by this study are the proprietary information of the Sponsor. Public disclosure of study data may include publication in a peer-reviewed journal.

12.13 Conflict of Interest Policy

Actual or perceived conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.

12.14 Abbreviations

ADSP	Adaptive Study Design Plan
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
ATP	Adenosine Triphosphate
AUC	Area Under the Concentration-Time Curve
[redacted]	[redacted]
[redacted]	[redacted]y
CFR	Code Of Federal Regulations
CI	Confidence Interval
C_{max}	Peak Concentration
CR	Complete Response
CRO	Contract Research Organization
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Event
[redacted]	[redacted]
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
EWOC	Escalation with Overdose Control

FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ILD	Interstitial Lung Disease
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous(ly)
IWRS	Interactive Web Response System
[redacted]	
LH	Luteinizing Hormone
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MTPI-2	Modified Toxicity Probability Interval-2
MUGA	Multi-gated Acquisition
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
PBPK	Physiologically Based PK
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PSA	Prostate Specific Antigen
QA	Quality Assurance
QC	Quality Control
QD	Once daily
QTc	corrected QT Interval
QTcF	QT Interval Corrected Using Fridericia's Formula
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
SoA	Schedule of Activities

SOP	Standard Operating Procedure
STD	Severely Toxic Dose
$T_{1/2}$	Half-life
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time to Peak Concentration
ULN	Upper Limit of Normal
WHO	World Health Organization

12.15 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
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		[redacted]	[redacted]
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		[redacted]	[redacted]
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Version	Date	Description of Change	Brief Rationale
V2.0	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]
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Version	Date	Description of Change	Brief Rationale
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		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
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Version	Date	Description of Change	Brief Rationale
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		[redacted]	[redacted]
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		[redacted]	[redacted]
		[redacted]	[redacted]

Version	Date	Description of Change	Brief Rationale
		~~and~~ appropriate treatment **should be** instituted as n[redacted]	
		[redacted]	[redacted]
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		[redacted]	[redacted]

Version	Date	Description of Change	Brief Rationale
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Version	Date	Description of Change	Brief Rationale
		Screening and every 2 cycles ~~(same with~~ [redacted]	
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]
		[redacted]	[redacted]

Version	Date	Description of Change	Brief Rationale
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		[redacted]	[redacted]
		[redacted]	[redacted]

Version	Date	Description of Change	Brief Rationale
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Version	Date	Description of Change	Brief Rationale
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Version	Date	Description of Change	Brief Rationale
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		[redacted]	[redacted]
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		[redacted]	[redacted]

Version	Date	Description of Change	Brief Rationale
		[redacted]	

Version	Date	Description of Change	Brief Rationale
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		[redacted]	[redacted]
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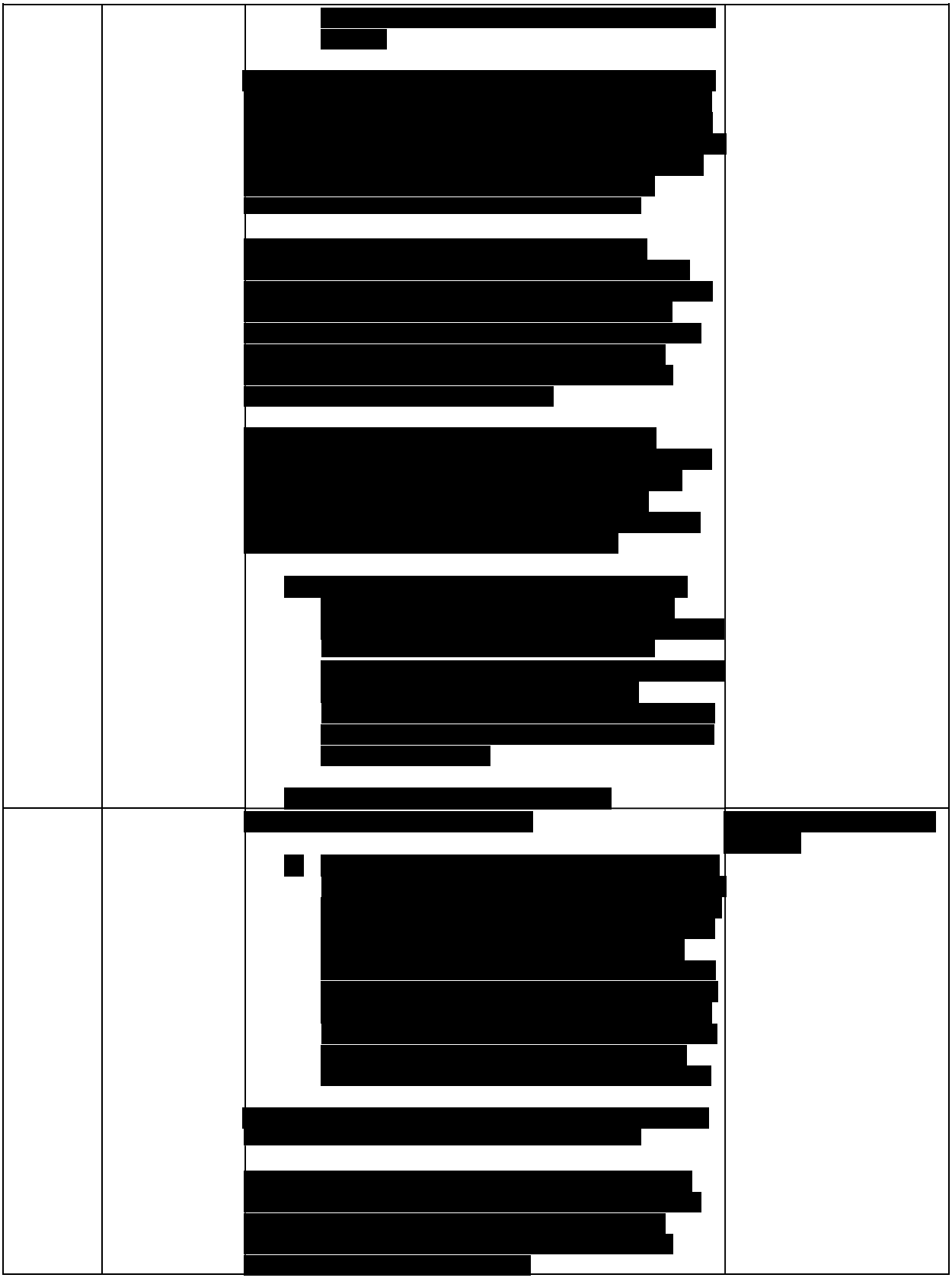
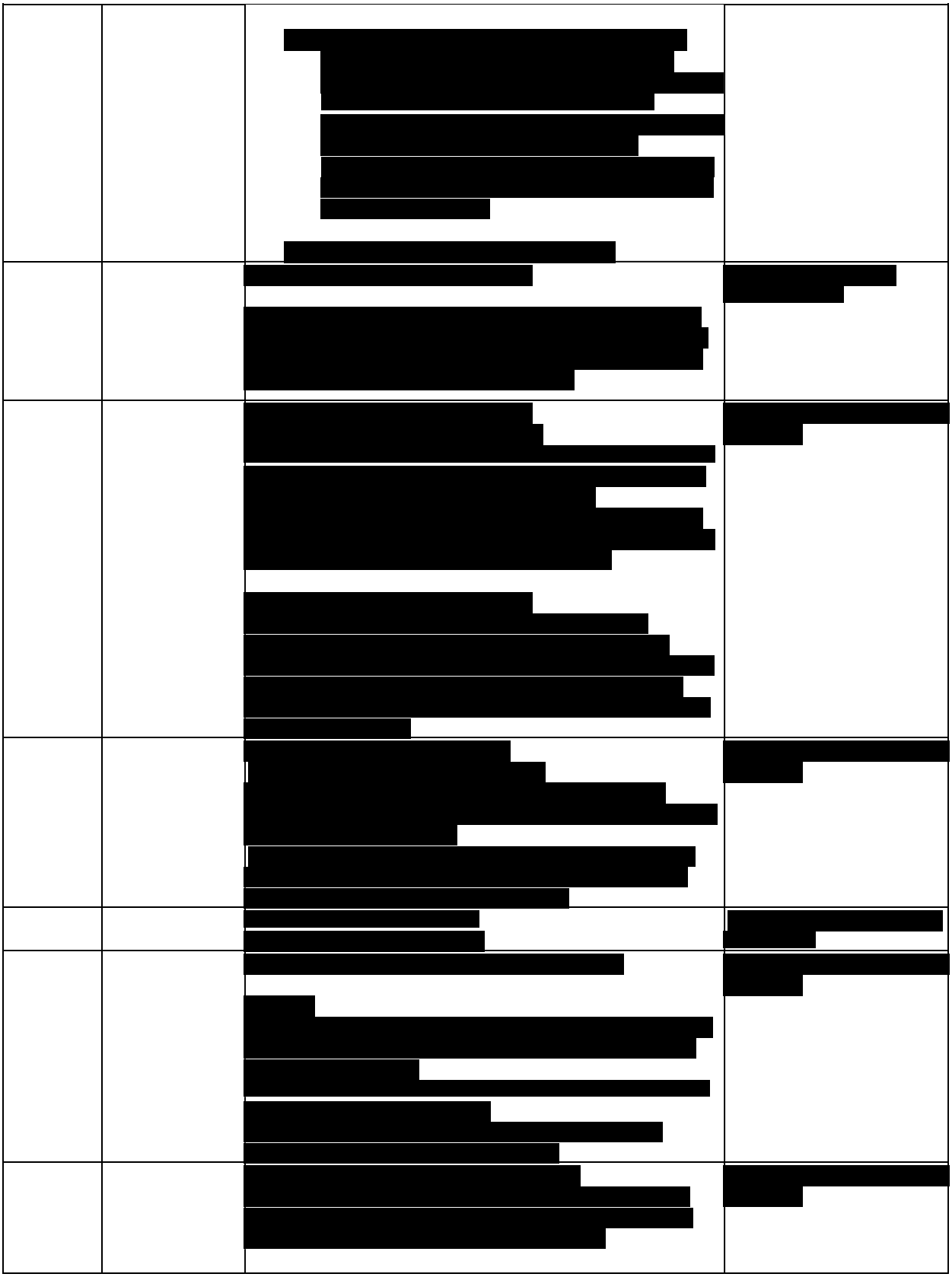
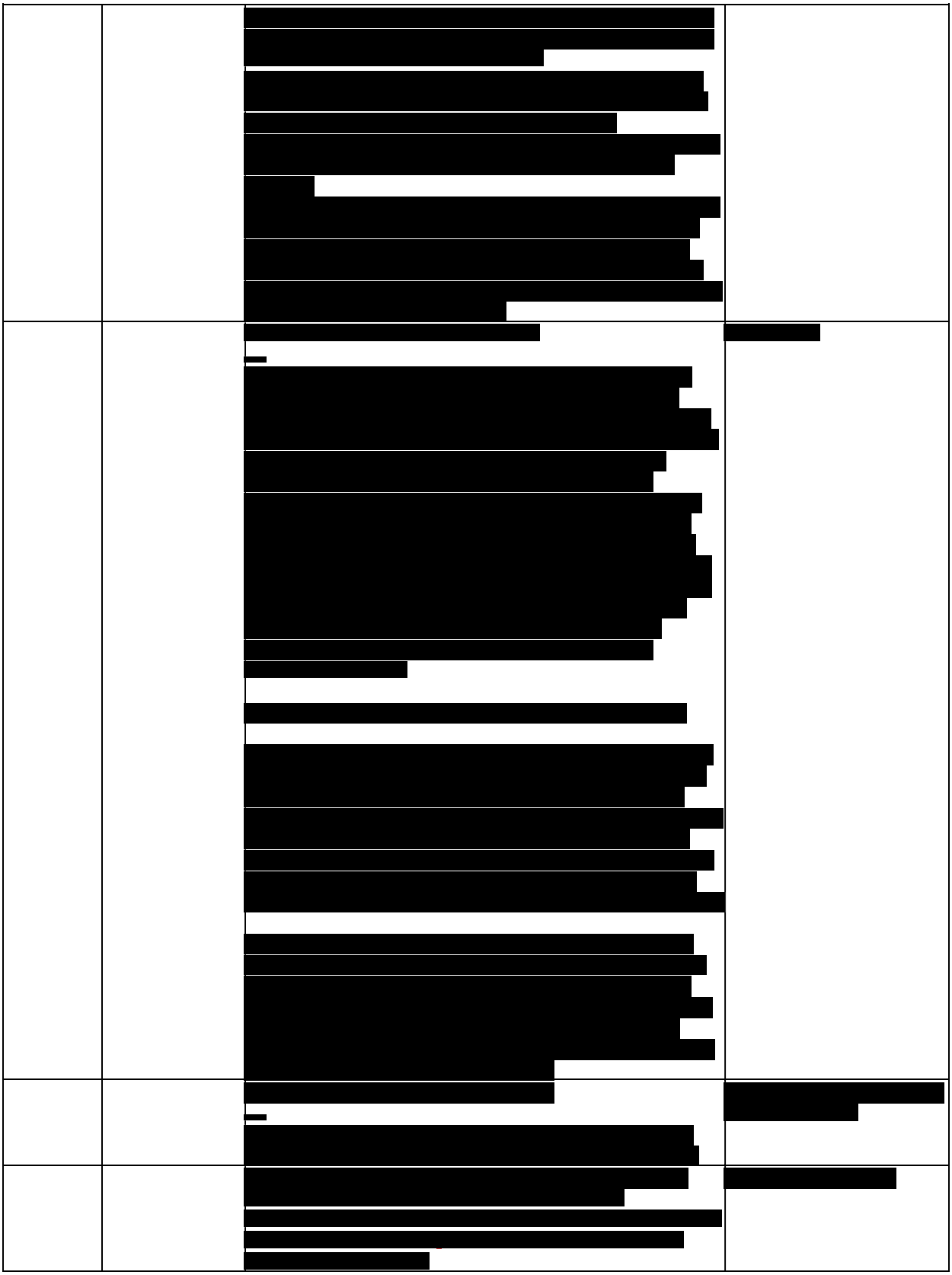
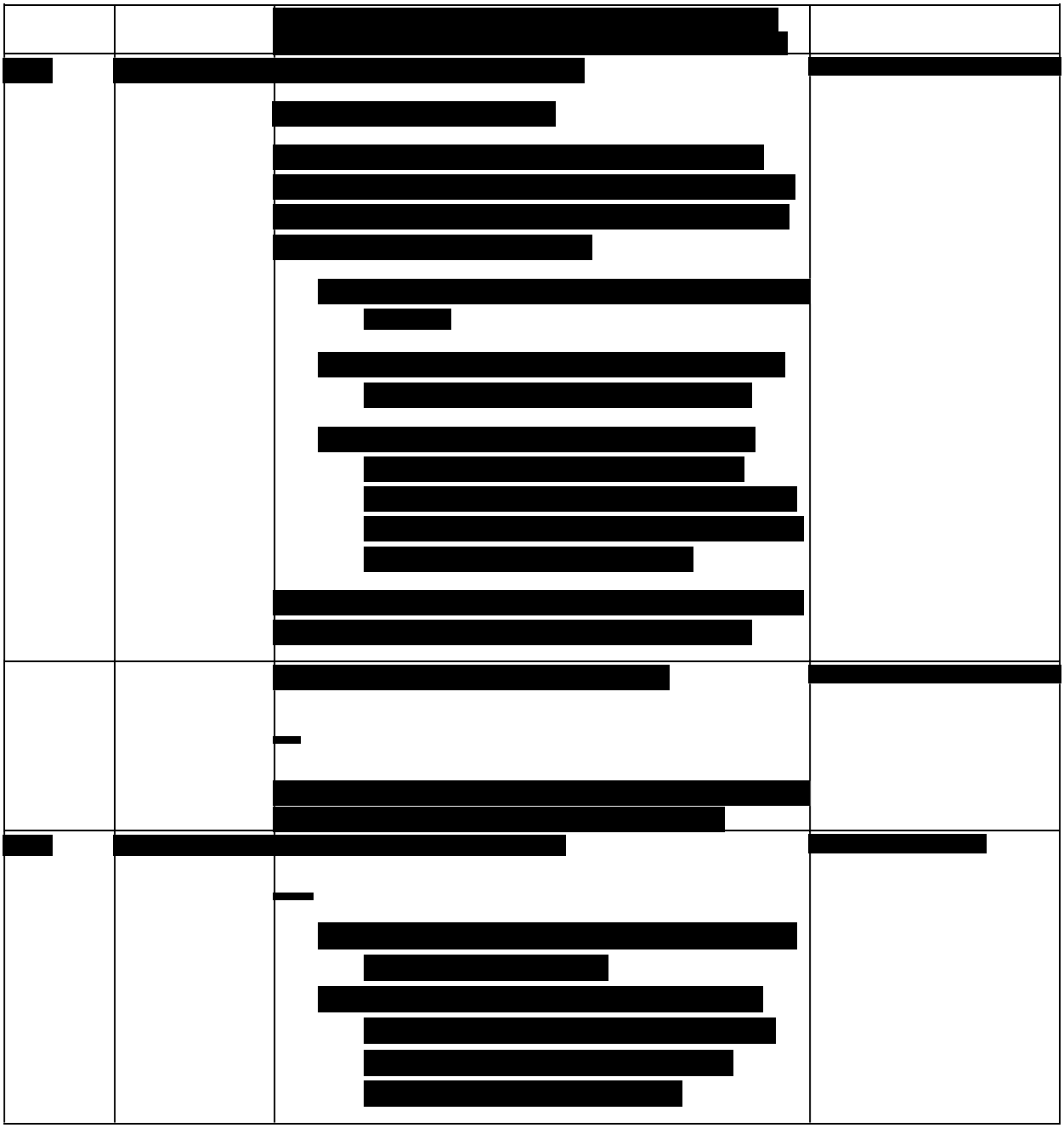
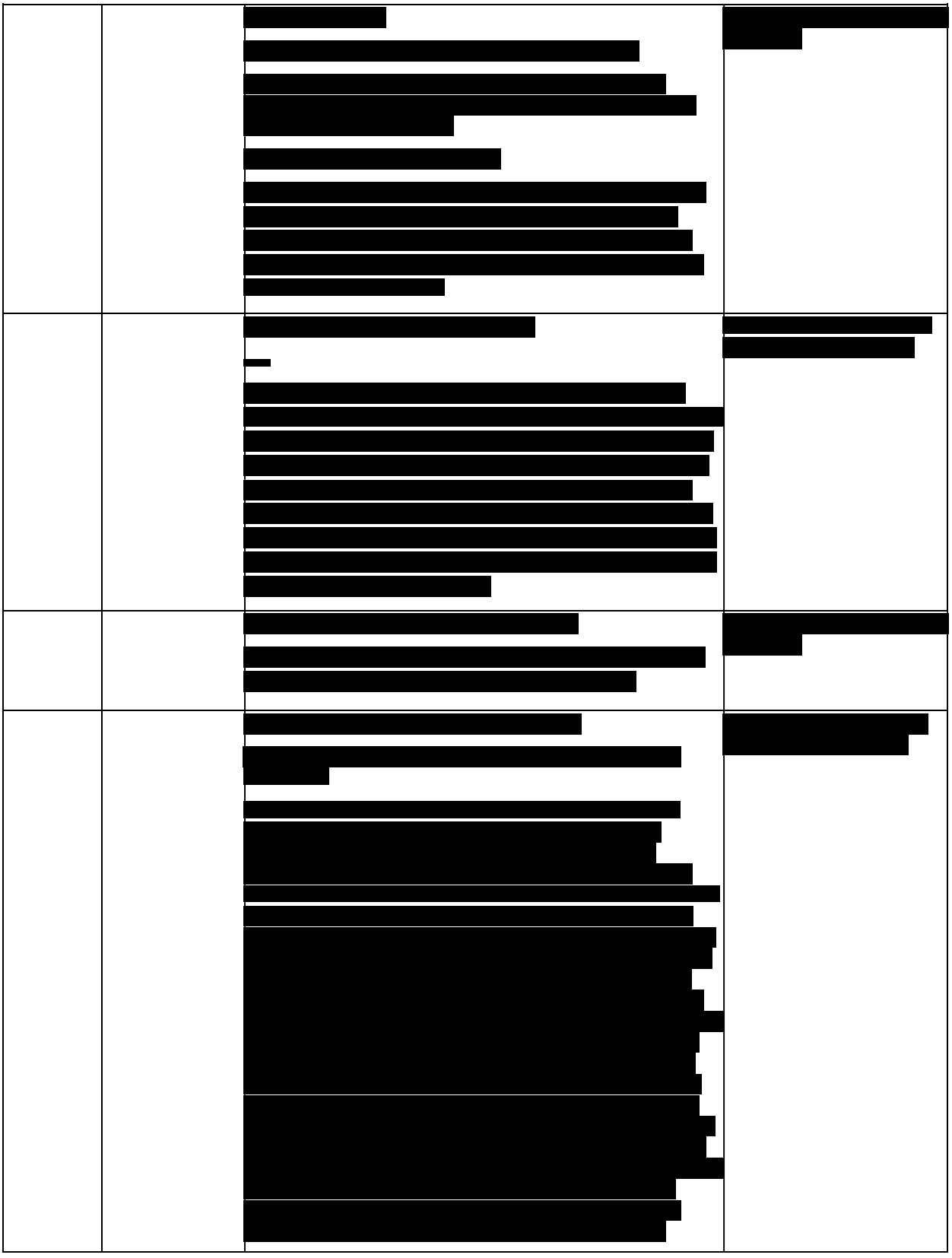


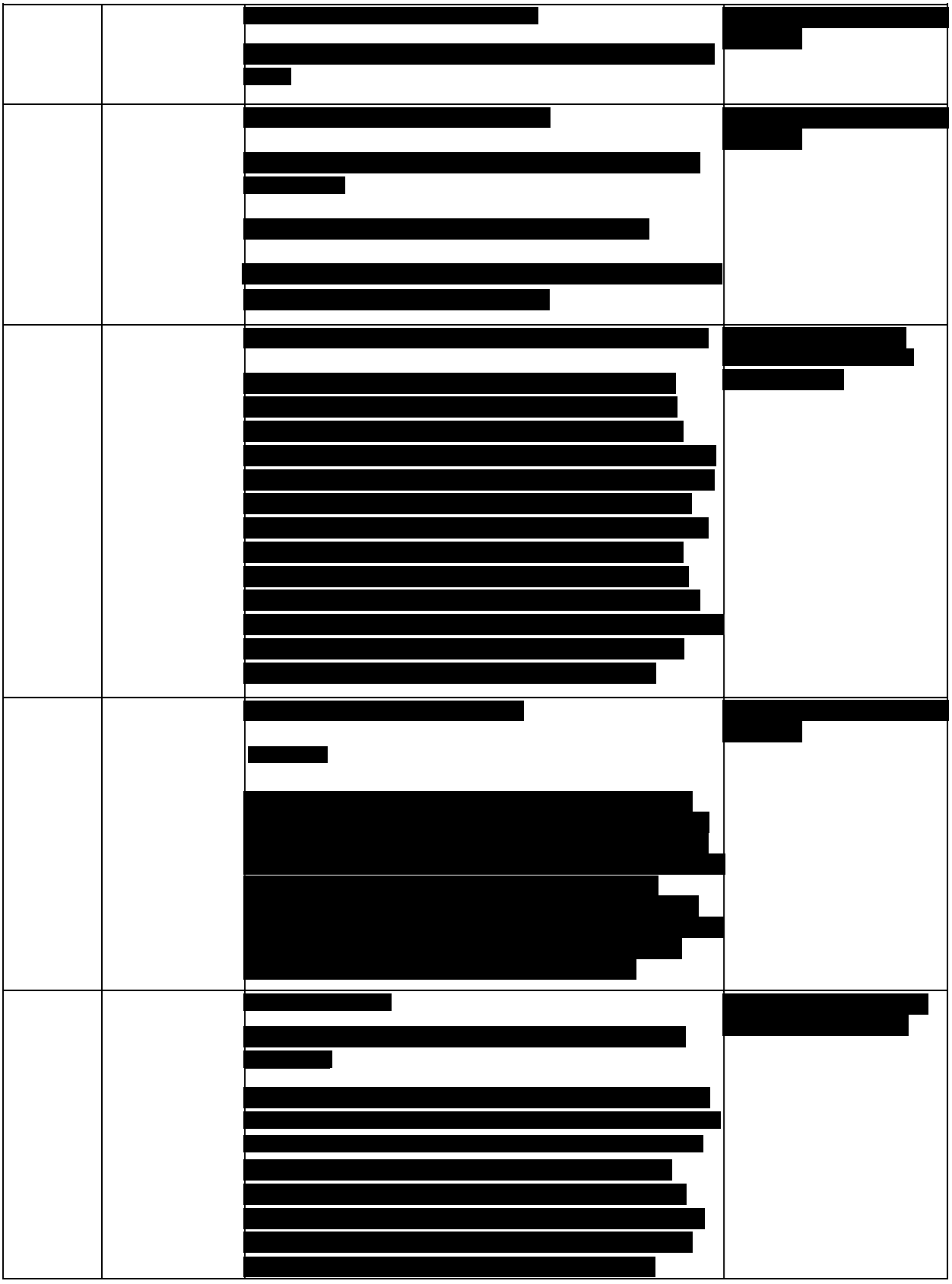


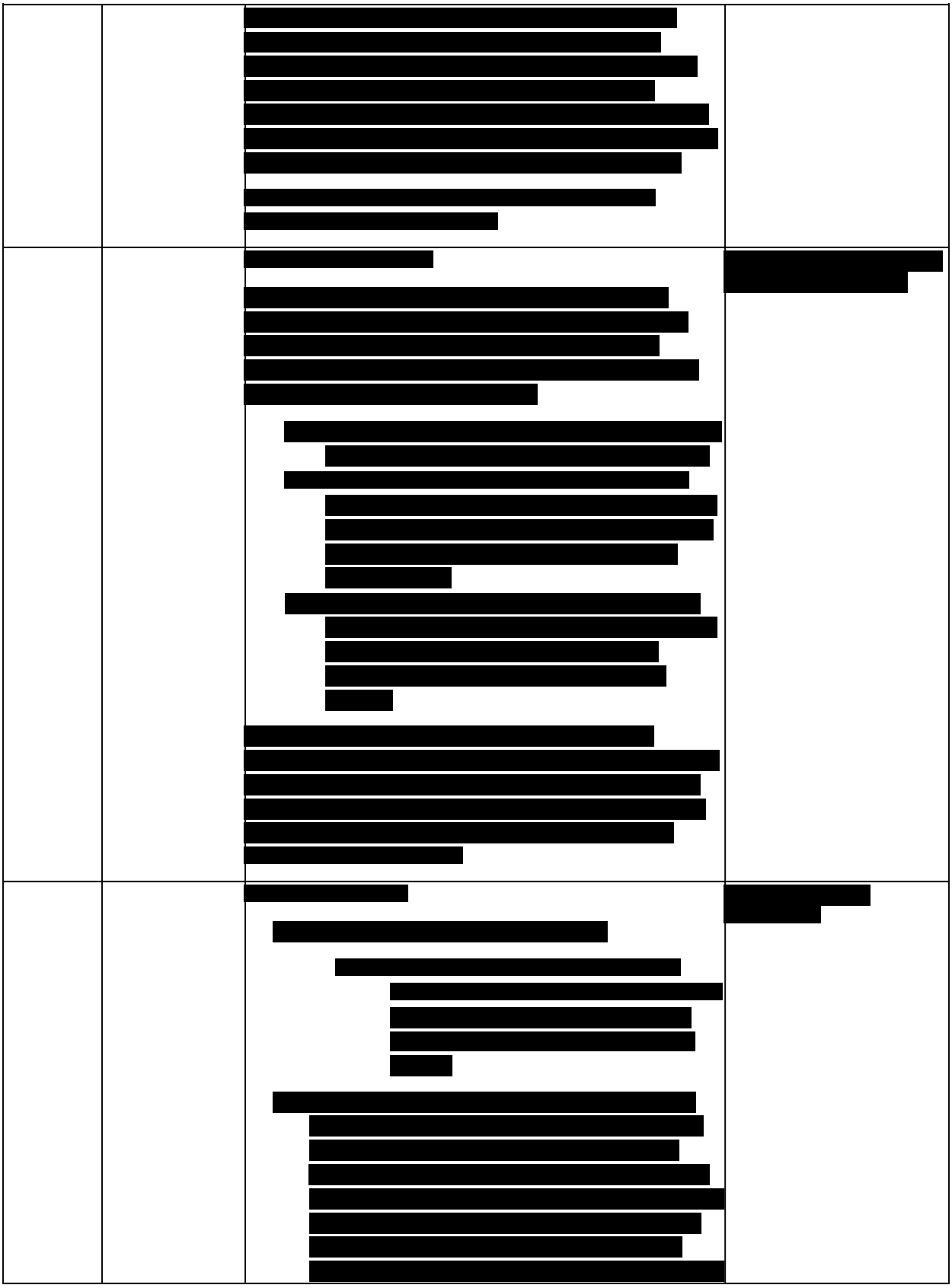


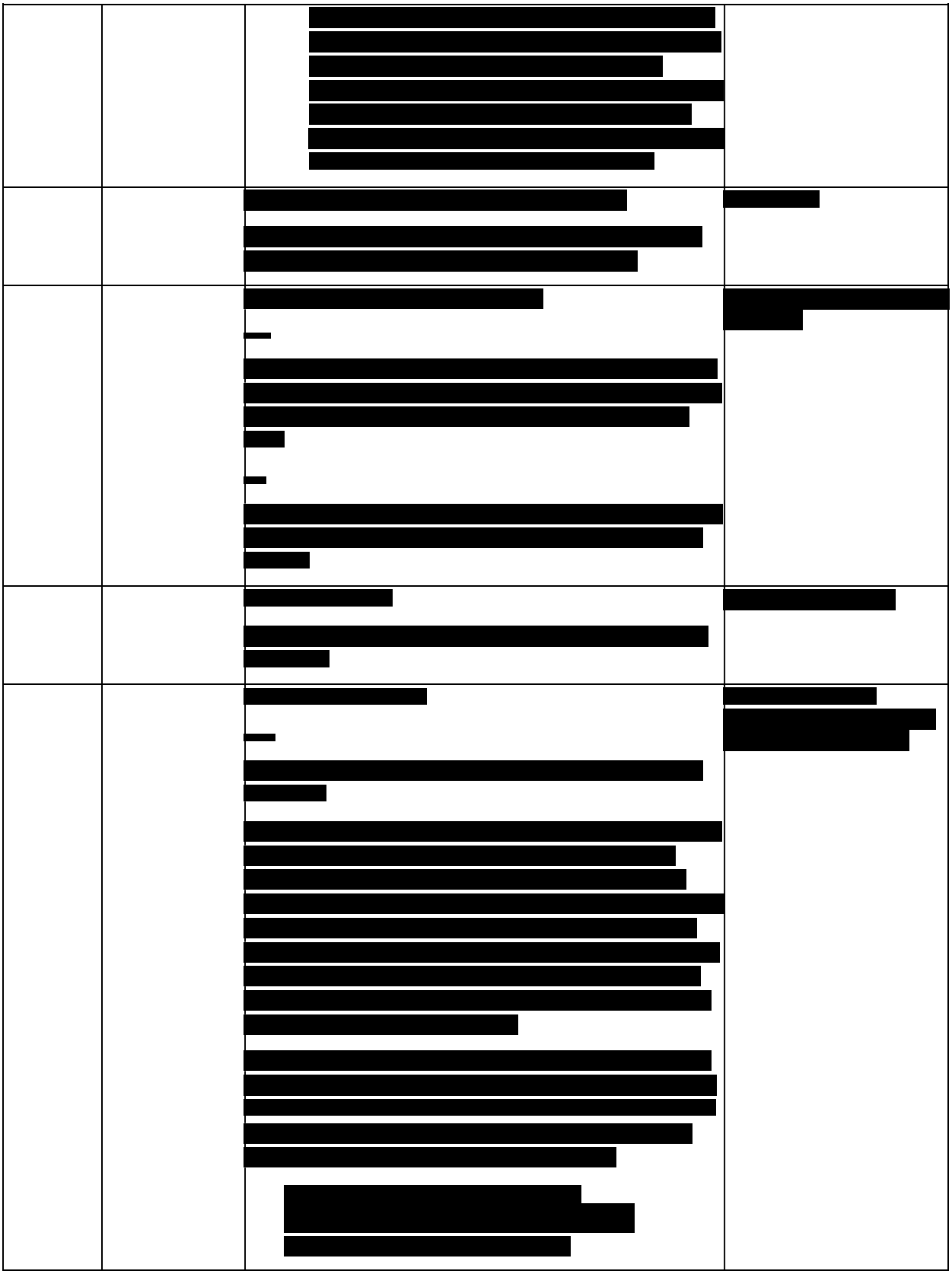


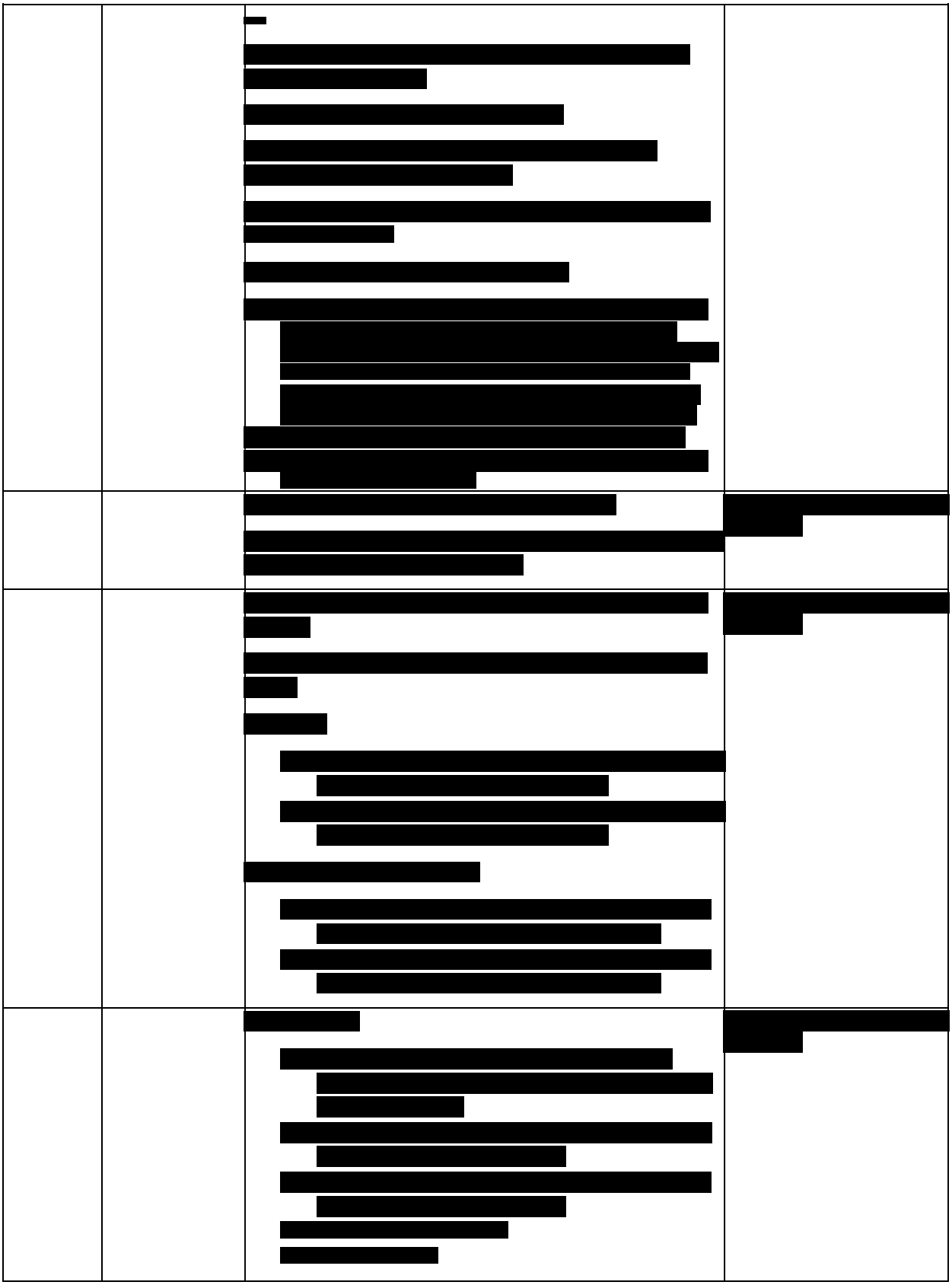
Version	Date	Description of Change	Brief Rationale











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13 REFERENCES

AstraZeneca Pharmaceuticals. Tagrisso (osimertinib) Prescribing Information. November 2015

Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011 Jul 20;29(21):2866-2874

Gettinger, Scott N., et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. *The Lancet Oncology* 2016; 17.12: 1683-1696

Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med.* 2015 Apr 30;372(18):1689-1699

Liu L, Liu J, Shao D, et al. Comprehensive genomic profiling of lung cancer using a validated panel to explore therapeutic targets in East Asian patients. *Cancer Sci.* 2017 Dec;108(12):2487-2494

Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009 Sep 3;361(10):947-957

Neuenschwander, Beat, Michael Branson, and Thomas Gsponer. Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*. 2008;27.13: 2420-2439

O'Quigley J, Pepe M, and Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics.* 1990 Mar;46(1):33-48

Piantadosi S, Fisher JD, and Grossman S. Practical implementation of a modified continual reassessment method for dose-finding trials. *Cancer Chemother Pharmacol.* 1998;41(6):429-36

Rangachari D, To C, Shpilsky JE, et al. EGFR-mutated lung cancers resistant to osimertinib through EGFR-C797S respond to first-generation reversible EGFR inhibitors but eventually acquire EGFR-T790M/C797S in preclinical models and clinical samples. *J Thorac Oncol*. 2019; Nov:14(11):1995-2002

Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2012 Mar;13(3):239-246

Rotow J and Bivona TG. Understanding and targeting resistance mechanisms in NSCLC. *Nat Rev Cancer.* 2017 Oct 25;17(11):637–658

Sequist LV, Soria JC, Goldman JW, et al. Rociletinib in EGFR -mutated non–small-cell lung cancer. *N Engl J Med.* 2015 Apr 30;372(18):1700-1709

Takeda Pharmaceutical Company Limited. Alunbrig (brigatinib) Prescribing Information. December 2018

Thress KS, Paweletz CP, Felip E, et al. Acqired EGFR C797S mediates resistance to AZD9291 in advanced non-small cell lung cancer harboring EGFR T790M. *Nat Med.* 2015 Jun;21(6):560-562

Wang Z, Yang JJ, Huang J, et al. Lung adenocarcinoma harboring EGFR T790M and in trans C797S responds to combination therapy of first and third generation EGFR-TKIs and shifts allelic configuration at resistance. *J Thorac Oncol*. 2017 Nov;12(11):1723−1727

Guo W, Wang SJ, Yang S, et al. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. *Contemp Clin Trials*. 2017;58:23-33

Razelle K, Chia-Chi L, et al. Moving Beyond 3+3: The Future of Clinical Trial Design *2021 ASCO EDUCATIONAL BOOK* May 2021; https:// doi.org/10.1200/ EDBK_319783

14 APPENDICES

Appendix 1. Signature of Investigator

Appendix 2. Eastern Cooperative Oncology Group (ECOG) Performance Status

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

Appendix 4. List of CYP3A4 Substrates With Narrow Therapeutic Index, CYP2C8 Strong Inhibitor, and P-gp Inhibitor

Appendix 5. Decision rules for dose escalation derived from the modified toxicity probability interval-2 (mTPI-2) method

Appendix 1. Signature of Investigator

Protocol Title: A Phase 1/2, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity of BBT-176 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) who Progressed Following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI) Agent

Protocol Number: BBT176-ONC-001

This protocol is a confidential communication of Bridge Biotherapeutics, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ **Date:** _____

Printed Name: _____

Name of Center: _____

Appendix 2. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol.1982;5:649-55.

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer.2009;45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 20 mm by chest X ray (if clearly defined and surrounded by aerated lung).

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non target lesions. Nodes that have a short axis < 10 mm are considered non pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

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

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded in the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has

visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient are known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best

response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR*	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; and NE = invaluable. See text for more details.

Note: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" in the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure that the identified responses are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the trial protocol.

Duration of Overall Response

The duration of overall response is measured from the time that measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria that are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The DoR and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment

periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

[redacted]