

CLINICAL STUDY PROTOCOL

Protocol Title: A First-in-Human, Phase 1a/1b, Open-Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients with Advanced or Refractory Tumors

Protocol Identifier: BGB-3245-AU-001

Phase: 1a/1b

Investigational Product: BGB-3245

Indication: Solid Tumors

Sponsor: MapKure, LLC
1840 Gateway Dr, 3rd Floor
San Mateo, CA 94404, United States

Sponsor Medical Monitor: 

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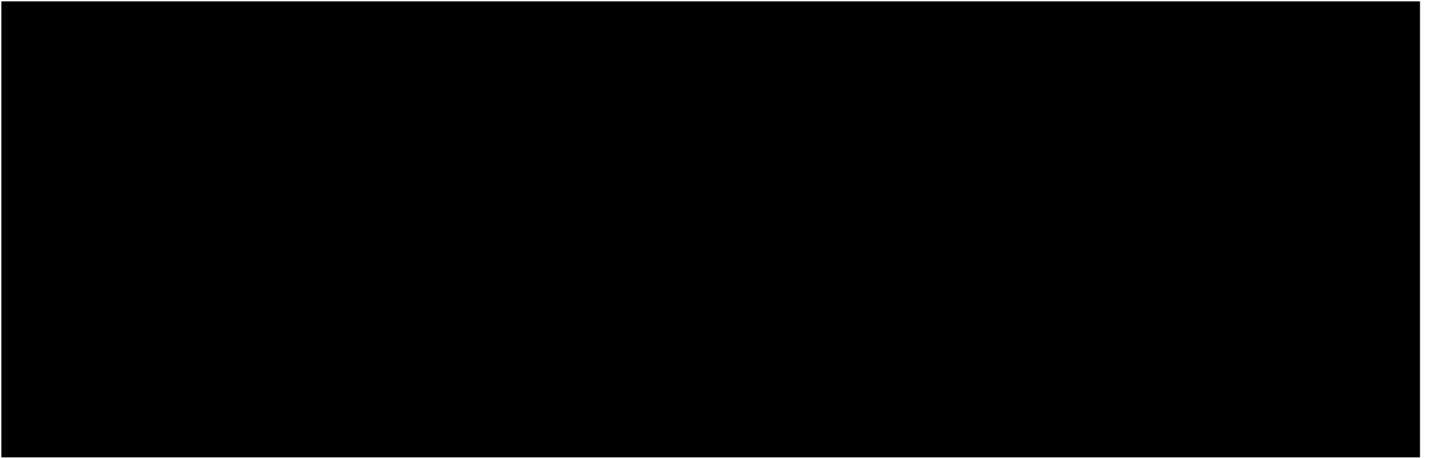
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FINAL PROTOCOL APPROVAL SHEET

A First-in-Human, Phase 1a/1b, Open-Label, Dose-Escalation and Expansion Study to
Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor
BGB-3245 in Patients with Advanced or Refractory Tumors

MapKure, LLC, Approval:



INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-3245-AU-001

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Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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PROTOCOL SYNOPSIS

Name of Sponsor	MapKure, LLC
Investigational Product	BGB-3245
Title of Study	A First-in-Human, Phase 1a/1b, Open-Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients with Advanced or Refractory Tumors
Protocol No.	BGB-3245-AU-001
Study Centers	Approximately 5 to 10 study centers globally
Phase	1a and 1b
Number of Participants	Approximately 28 to 60 participants in Phase 1a dose escalation were planned to be enrolled and up to approximately 105 participants (to achieve up to 75 evaluable in the expansion cohorts) in Phase 1b may be enrolled; up to 15 efficacy evaluable participants with v-RAF murine sarcoma viral oncogene homolog B (BRAF) fusion mutation tumors. The actual sample size will depend on the number of dose-escalation cohorts enrolled.
Study Duration	This study will consist of 3 periods: 1. Screening Period represents the 28 days between the date of signing the informed consent until the first administration of study drug. 2. Treatment Periods for Phase 1a and Phase 1b will be as follows: a. In Phase 1a, the first treatment cycle was 30 days, with a 2-day treatment-free period on Days 2 and 3. After the first treatment cycle, participants were treated by repeated treatment cycles of 28 days. In Phase 1b, all treatment cycles will be 28 days of continuous BGB-3245 treatment. b. All participants will receive study drug until 1) disease progression; 2) cessation of study treatment due to death, intolerance, or withdrawal of consent from the study; 3) completion of 2 years of treatment (unless the investigator's benefit-risk assessment supports continued treatment); 4) Investigator's decision; or 5) the study is stopped by the sponsor for any reason. 3. Safety Follow-up Period consists of a follow-up visit at approximately 30 (+ 7) days after the last dose of the study drug. a. Beyond 30 days, investigators should report any serious adverse events (SAEs) that are believed to be related to study drug or deaths irrespective of the cause if they become aware of them. b. Ongoing adverse events (AEs) considered related to study treatment will be followed until the event has resolved to baseline or Grade ≤ 1, the event is assessed by the investigator as stable, the participant is lost to follow-up, the participant

	withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.
Study Objectives Phase 1a Primary - To assess the safety and tolerability of BGB-3245 in participants with solid tumors. - To determine the maximum tolerated dose (MTD), if any, and recommended Phase 2 dose (RP2D) for BGB-3245. Secondary - To characterize the pharmacokinetics (PK) of BGB-3245 after single-dose and multiple-dose administration. - To assess the preliminary antitumor activity of BGB-3245. Exploratory - To determine potential predictive biomarkers of molecular response. - To assess potential pharmacodynamic (PDx) biomarkers of target engagement, biological activity, and mechanism of action. - To explore mechanisms of treatment resistance in participants who fail to respond or develop resistance. Phase 1b Primary - Evaluate the optimal RP2D for BGB-3245 - To determine the objective response rate (ORR) as assessed by initial investigator review using Response Evaluation Criteria in Solid Tumors (RECIST version [v] 1.1) of BGB-3245 at the RP2D when given orally in participants with mutational selected solid tumors. - To further clarify the ORR as assessed by investigator review using RECIST v1.1 of BGB-3245 in participants with tumors harboring BRAF fusions Secondary - To determine the progression-free survival (PFS); disease control rate (DCR) as assessed by initial investigator review using RECIST v1.1; duration of response (DOR); clinical benefit rate (CBR); and overall survival (OS) of BGB-3245 as a single agent. - To further assess the safety and tolerability of BGB-3245. - To further characterize the PK of BGB-3245. Exploratory - To determine potential predictive biomarkers of molecular response. - To assess potential PDx biomarkers of target engagement, biological activity, and mechanism of action. - To explore mechanisms of resistance in participants who fail to respond or develop resistance.	
Study Population Inclusion Criteria Each participant eligible to participate in this study must meet all of the following criteria:	

1. Participants have voluntarily agreed to participate by giving written informed consent and must be ≥ 18 years of age on the day of signing the informed consent form.
2. Participants with histologically confirmed advanced or metastatic solid tumor who had disease progression during or after systemic anticancer therapies that previously demonstrated clinical benefit (eg, improved survival) in a representative population, or are unable to receive standard therapy(ies). In addition, participants must meet the following eligibility criteria for the corresponding phase of the study:
 - a. Phase 1a: Participants with a known mutation status and tumor harboring an oncogenic mutation of the BRAF gene (the mutations of primary interest are the BRAF Class II mutation, Class III mutation, or BRAF fusion). In addition, participants with tumors harboring the mutation of the neuroblastoma RAS viral oncogene homolog (NRAS) gene or the Kirsten rat sarcoma virus oncogene (KRAS) are eligible for Part 1a. For participants with KRAS mutations, tumor types of CRC and pancreatic cancer are excluded.
 - b. Phase 1b: Participants must have a known mutation status as assessed by local testing and meet 1 of the following criteria according to the group they are enrolled into:
 - i. Group 1: Participants with tumor types other than CRC that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition
 - ii. Group 2: Participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation.
 - iii. Group 2 BRAF Fusion Expansion: Participants with advanced solid tumors harboring a BRAF fusion mutation
3. Participants must provide archival tumor tissue or a fresh tumor biopsy for mutation status and biomarkers analysis. Fresh tumor biopsies are strongly recommended at Screening in participants with readily accessible tumor lesions.

Note: Local analysis of the mutational status is required for meeting inclusion criterion #2. Tumor samples will be used to confirm mutation status by central laboratory assessment (see exceptions noted in [Section 7.5](#)).

4. Participants must have radiologically measurable disease as defined per RECIST v1.1.
5. ECOG performance status of ≤ 1 at Screening.
6. Life expectancy ≥ 12 weeks at Screening.
7. Adequate hematologic and organ function as indicated by the following laboratory values prior to Cycle 1 Day 1:
 - a. absolute neutrophil count (ANC) ≥ 1500 cells/ μ L
 - b. Platelet count $\geq 100,000$ / μ L
 - c. Hemoglobin ≥ 8 g/dL
Note regarding hematologic function: Participant must not have received blood transfusion or growth factor support ≤ 14 days before the sample collection
 - d. Estimated creatinine clearance ≥ 50 mL/min by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see Appendix 16.8 for calculation)
 - e. Total bilirubin (TBIL) $\leq 1.5 \times$ upper limit of normal (ULN) (TBIL must be $\leq 3 \times$ ULN for participants with Gilbert's syndrome)

- f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ for participants with liver metastases
- 8. Adequate cardiac function, as determined by:
 - a. Systolic blood pressure < 160 mmHg and diastolic blood pressure < 100 mmHg (Grade ≤ 2)
 - b. Left ventricular ejection fraction $\geq 50\%$ by echocardiogram or multiple-gated acquisition
 - c. No clinically significant electrocardiogram (ECG) waveform abnormalities
 - d. Corrected QT interval by Fridericia's correction (QTcF) ≤ 470 ms, as determined by the mean QTcF values from the ECG assessments at screening (one triplicate).
- 9. Female participants are eligible to enter and participate in the study if they are of:
 - a. Nonchildbearing potential as defined in Appendix 16.4
 - b. Childbearing potential as defined in Appendix 16.4, have a negative serum pregnancy test at Screening (within 7 days of the first dosing of study drug), and use contraception (as defined in Appendix 16.4) before study entry and throughout the study until 180 days after the last dose of the study drug
- 10. Male participants are eligible to enter and participate in the study if they are vasectomized or agree to use of contraception (as defined in Appendix 16.4) during the study treatment period and for at least 180 days after the last dose of the study drug.

Exclusion Criteria

Participants who meet any of the following criteria must be excluded from this study:

- 1. Female participants who are pregnant or lactating.
- 2. Participants receiving cancer therapy (chemotherapy or other systemic anticancer therapies, immunotherapy, radiation therapy, or surgery) at the time of Cycle 1 Day 1.
- 3. All participants who have received prior systemic anticancer treatment within the following time frames will be excluded:
 - a. Systemic chemotherapy within 4 weeks, or 6 weeks for nitrosourea, mitomycin C, prior to Cycle 1 Day 1; and
 - b. Biologic therapy (ie, antibodies), continuous or intermittent small-molecule therapies, or any other investigational agents within a period of 5 times the half-life of the agent or ≤ 4 weeks (whichever is shorter) prior to Cycle 1 Day 1
- 4. Active infection requiring systemic treatment at the start of the study treatment.
- 5. Any of the following cardiovascular criteria:
 - a. Current evidence of unstable angina or another form of symptomatic cardiac ischemia
 - b. Symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease ≤ 6 months before Cycle 1 Day 1
 - c. Acute myocardial infarction ≤ 6 months prior to Cycle 1 Day 1
 - d. Heart failure of New York Heart Association (Appendix 16.5) Classification III or IV ≤ 6 months prior to Cycle 1 Day 1
 - e. Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Cycle 1 Day 1
 - f. Cerebral vascular accident or Grade ≥ 2 transient ischemic attack ≤ 6 months prior to Cycle 1 Day 1

- g. Grade ≥ 2 hypertension: that cannot be managed by standard antihypertension medications before Cycle 1 Day 1
 - h. Syncope or seizure ≤ 6 months before Cycle 1 Day 1
- 6. Any major surgery within 28 days prior to Cycle 1 Day 1.
- 7. Participants with toxicities that have not recovered to Grade ≤ 1 or stabilized, except for alopecia and those Grade 2 toxicities listed as permitted in the other eligibility criteria. Grade 2 neuropathy or isolated asymptomatic Grade 2 laboratory abnormality without clinical correlation may be acceptable at the investigator's discretion after consultation with the medical monitor.
- 8. Immune-related reactions such as pneumonitis, colitis, hepatitis, or myocarditis that did not resolve after discontinuation of prior checkpoint inhibitor use.
- 9. History or presence of gastrointestinal disease or other condition known to interfere with the absorption of drugs.
- 10. History of allergy or hypersensitivity to BRAF inhibitors or combination therapies including BRAF inhibitors.
- 11. Current evidence of symptomatic central nervous system (CNS) metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Asymptomatic treated or asymptomatic untreated brain metastases are allowed as long as participants are clinically stable in the judgment of the investigator.
 - a. Participants must have a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain or spinal regions (as applicable to the CNS involvement) at Screening to confirm the stable status of the above CNS metastases
 - b. The neurological symptoms of the above CNS metastases must be stable without the use of steroids ≥ 14 days before the start of the study treatments
 - c. Participants must have no CNS surgery or radiation (except prophylactic cranial irradiation, where indicated) ≤ 28 days before Cycle 1 Day 1 and no stereotactic radiosurgery ≤ 14 days before Cycle 1 Day 1
- 12. Any active malignancy ≤ 3 years before Cycle 1 Day 1 except for the specific cancer under investigation in this study and any localized cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
- 13. Any participant with a solid organ transplant requiring antirejection medications.
- 14. Any unstable, preexisting major medical condition that in the opinion of the investigator contraindicates the use of a study drug, including known human immunodeficiency virus (HIV) or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
 - a. Participants who are hepatitis B surface antigen (HBsAg) positive or HCV antibody positive at Screening may be enrolled only if HBV DNA titers < 500 IU/mL or negative HCV RNA polymerase chain reaction test, respectively
 - b. Participants who have HIV infection at Screening may be enrolled only if CD4+ T-cell (CD4+) counts ≥ 350 cells/ μ L

15. Psychological, familial, sociological, or geographical conditions that are likely to interfere with compliance with the protocol.
16. Unfit for the study, in the opinion of the investigator, after medical interview, physical examination, or screening investigations.
17. Receiving any of the prohibited medications listed in [Section 6.1](#) or will require any of these medications.
18. Concurrent participation in another therapeutic clinical trial.
19. Receiving any treatment with a strong CYP3A4 inhibitor or inducer ≤ 14 days (or 5 half-lives, whichever is longer) before Cycle 1 Day 1, as outlined in [Section 6.2](#).

Test Product, Dose, and Mode of Administration

BGB-3245 will be administered orally, once daily (QD).

Phase 1a Planned Dose Levels

- Level 1: BGB-3245, 5 mg
- Level 2: BGB-3245, 10 mg (100% increase)
- Level 3: BGB-3245, 15 mg (50% increase)
- Level 4: BGB-3245, 25 mg (67% increase)
- Level 5: BGB-3245, 40 mg (60% increase)
- Level 6: BGB-3245, 60 mg (50% increase)
- Subsequent Dose Levels: TBD

The Safety Monitoring Committee (SMC) could have recommended dose levels above or below these dose levels, and additional doses and/or dosing schedules could have been considered based on the safety, tolerability, and efficacy observed during dose escalation (eg, BGB-3245 at 80 mg QD or higher), including steps of 5 mg. An intermediate, not predefined, previously evaluated or not previously evaluated dose, or a less-frequent dosing schedule that did not exceed the MTD level (based on steady-state exposure) could have been considered if evaluation of AEs at such a dose or schedule is desired.

Phase 1b

The sponsor will make a recommendation on the selection of the BGB-3245 dose or doses and regimen(s) to be used in Part 1b (RP2D) based on available safety, efficacy, PK, and exploratory data from Phase 1a. The RP2D selection will be reviewed and confirmed by the SMC based on the review of all available data. This will be further evaluated in the Phase 1b portion of the study in Group 1 by studying the 25-mg and 40-mg doses to determine the RP2D in 20 participants/dose level. The review will include an evaluation of the safety of BGB-3245 in the various groups and the ORR as defined in the protocol.

Study Design

This is a multicenter, open-label, Phase 1a/1b (dose-escalation and expansion) study of BGB-3245 in participants with tumors harboring BRAF or KRAS/NRAS/HRAS mutations that may respond to a rapidly accelerated fibrosarcoma (RAF) dimer inhibitor.

Baseline tumor tissue is mandatory for mutation status and biomarker analysis. Baseline tumor tissue can be derived from either archived tumor tissue or from fresh tumor biopsies prior to initiation of study treatment.

For Part A, for participants who have readily accessible tumor lesions and who consent to the biopsies, an optional follow-up biopsy may be taken, ideally from the same tumor lesion, for the analysis of PDx biomarkers.

For Part B, for participants who have readily accessible tumor lesions, and who consent to the biopsies, an optional fresh tumor biopsy will be performed at the time of discontinuation of the study drug. Fresh biopsies are optional at the time of treatment discontinuation and require additional written consent.

In addition, blood samples will be collected from all participants for mutation status and biomarker analysis.

Tumor Mutation Testing

Participants will be selected for screening and eligibility based on known mutation status through the local molecular testing obtained from the tumor tissue sample collected any time prior to screening. The mutation result from the local molecular testing assay for both Phase 1a and Phase 1b must be confirmed by a central analysis testing assay. Confirmatory mutation testing should be performed at a central laboratory at any time during the study to support the study data analysis. When possible, the tumor sample tested locally should be the same as the sample tested centrally. Definitive central laboratory mutation results (positive or negative) cannot be repeated. If a sample is determined to be inadequate or the result is indeterminate on central testing, an additional sample may be resubmitted to the laboratory for retesting. If there is non-concordance between the local and central laboratory results, or if the local result cannot be confirmed by central laboratory (eg, inadequate sample or poor sample quality), participants may continue receiving study treatment provided there is no clinical deterioration or disease progression and the participant is benefiting from study treatment, as determined by the investigator and in consultation with the medical monitor. In such cases, participants will be informed as soon as possible that their mutation status is unconfirmed with information to describe follow-up procedures and alternative treatment options.

Phase 1a

Dose cohort size management and dose-escalation decisions were made in accordance with the modified toxicity probability interval-2 (mTPI-2) design and had to be confirmed by the SMC.

The mTPI-2 used a Bayesian statistics framework and a beta-binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflected the relative difference between the toxicity rate of each dose level. The target toxicity rate for the MTD was $\phi = 0.30$. The maximum sample size was to be 60 participants. The Phase 1a portion of the trial enrolled and treated participants in minimum cohorts of 3 participants. Being a model-assisted design, mTPI-2 automatically and appropriately tailors dose-escalation and de-escalation- decisions with the acceptable toxicity probability interval of (0.25, 0.33).

Cohorts of participants could have received doses already tested but a dose that was associated with decision “Dose de-escalate, unacceptable toxicity” could not have been revisited and no additional participants should have been treated at this dose or higher doses for the remainder of the trial.

The starting dose was 5 mg/day (5 mg QD). The 30-day initial treatment cycle (Cycle 1) of each dose level cohort consisted of a single administration of BGB-3245 on Day 1, followed by a 2-day treatment-free period (Days 2 and 3) and a 27-day period of repeated drug administration (Days 4 to 30).

Periodic safety evaluations were performed by the SMC at the milestones defined by the mTPI-2 model, or more frequently if warranted by the treatment-emergent data. The SMC, which consists of sponsor’s representatives, contract research organization’s medical monitor, and at least 2 participating investigators, was established for the determination of the dose levels to be administered, and the dose regimen adjustments(s), during dose escalation, based on available data from the current and previous dose levels. Evaluation of a cohort of at least 3 participants completing 1 cycle of treatment at that dose

level was required prior to determining the dose level and dose regimen for the next cohort. The RP2D and dosing regimen to be used in Phase 1b were to be recommended by the sponsor and confirmed by the SMC and were to be based on all available safety, preliminary efficacy, PK, and exploratory data from Phase 1a. The sponsor, in consultation with the SMC, may evaluate dose levels and/or schedules that have not been predefined or eliminated. At the time of completion of the Phase 1a portion of this study, the RP2D and dosing regimen were not recommended. For the Phase 1b portion of the study, 2 dosing regimens are being evaluated.

Phase 1b

Phase 1b is a multicenter, open-label, parallel-design, dose expansion study. The Phase 1b part of the study will investigate RP2D(s) to examine the potential efficacy as well as safety and tolerability of BGB-3245 in several solid tumor indications. Enrollment of participants will proceed using an Interactive Response Technology (IRT) system. Phase 1b participants will be randomized to a dose cohort by the IRT. The following treatment groups will be enrolled in the dose expansion cohort:

- Group 1: Participants with tumor types other than CRC that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition (n=40 evaluable participants).
 - Participants will be randomized via IRT to receive either 25 mg QD or 40 mg QD dose of BGB-3245 for a total of 20 participants/dose level. The RP2D will be determined based on the safety, efficacy, tolerability, and the PK of the 2 dose levels.
- Group 2: Participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation (n=20 evaluable participants).
 - Examples of Class II mutations include P367L/S, G464V/E, G469V/S/R/I/A/T170delinsAK, L485W/F, N486_A489delinsK, N486_P490del, L525R, E586K, L597V/S/R/Q/P/K, A598V/T599insV, T599I/dup/V600insT, T599I/K, T599TT/TS, V600_K601D/E/N, V600_K601del, V600_K602delinsDT, V600_W604delinsDQTDG, K601_S602delinsNT, K601E/N/T, BRAF kinase duplication. Additional Class II mutations considered upon medical monitor approval.
 - Participants in Group 2 BRAF Fusion will be treated with 40 mg QD dose of BGB-3245.
 - Treatment will be managed via the IRT system.
- Group 2 BRAF Fusion Expansion: Participants with advanced solid tumors harboring a BRAF fusion mutation (up to n=15 evaluable participants).
 - Participants in Group 2 will be treated with 40 mg QD dose of BGB-3245
 - Treatment will be managed via the IRT system.

Definition of an evaluable participant for Phase 1b and details of the statistical assessment are provided in [Section 9.1.6](#) of the protocol.

Safety in Phase 1a and Phase 1b

During the treatment period in both parts of the study, participants will be monitored for safety, tolerability, and efficacy throughout the study from the day of first administration of study drug up to 30 (+ 7) days after the last administration of the study drug.

Dose-Limiting Toxicities

All toxicities or AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version (v) 5.0. The occurrence of any of the following

toxicities will be considered a dose-limiting toxicity (DLT) during dose escalation if it occurs within 30 days of receiving BGB-3245 on Cycle 1 Day 1, with the exclusion of toxicities clearly related to disease progression or intercurrent illness.

Hematologic

1. Any Grade ≥ 4 hematological toxicity
2. Grade ≥ 3 febrile neutropenia (defined as ANC $< 1000/\text{mm}^3$ with a single temperature $> 38.3^\circ\text{C}$ (101°F) or a sustained temperature $\geq 38^\circ\text{C}$ (100.4°F) for > 1 hour)
3. Grade 3 neutropenia lasting > 7 days
4. Grade 3 thrombocytopenia with clinically significant bleeding

Nonhematologic

1. Any death not clearly due to the underlying disease or extraneous causes and for any toxicity requiring permanent discontinuation of study drug(s)
2. Any Grade ≥ 4 nonhematologic event unless otherwise noted below
3. Grade ≥ 3 total bilirubin (except in participants with Gilbert's Syndrome) or transaminases (ALT or AST)
4. Confirmed occurrence of Hy's law or the United States Food and Drug Administration's definition of potential drug-induced liver injury not explained by any other cause(s) (eg, viral hepatitis, exposure to other hepatotoxins), without evidence of cholestasis and include the following laboratory abnormalities:
 - Participants with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values $\geq 3 \times \text{ULN}$ concurrent with a total bilirubin value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $\leq 2 \times \text{ULN}$ or other findings indicating an absence of cholestasis
 - For participants with baseline ALT or AST values above the ULN, AST or ALT value $\geq 2 \times$ the baseline values should be used in the definition mentioned above

Note that this specific category of DLT uses ULN rather than CTCAE grade for definition.
5. Grade ≥ 3 rash that did not begin to resolve within 7 days of initiating optimal medical and supportive care
6. Grade ≥ 3 significant neurologic toxicity (eg, seizure, hallucination, confusion, or delirium)
7. Grade ≥ 3 generalized muscle weakness
8. Grade ≥ 3 creatine phosphokinase with or without symptoms
9. Grade ≥ 3 nonhematologic treatment-related toxicity not listed above that did not resolve to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy

Clinically important or persistent toxicities that are not included above may also be considered a DLT following review by the sponsor in consultation with investigators or following review by the SMC. Additionally, any clinically significant toxicities that occur after the DLT observation period for a given dose level may be taken into account regarding subsequent dose escalation and/or RP2D decisions.

The following toxicities will not be considered a DLT:

- Isolated Grade 3 or Grade 4 laboratory abnormalities not listed above that have no clinical correlation and resolve to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy

- Grade ≥ 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 within 3 days
- Grade ≥ 3 fatigue that resolves to Grade ≤ 1 within 5 days
- Grade ≥ 3 asymptomatic increase of lipase or amylase without pancreatitis that resolves to Grade ≤ 1 within 3 days

In such cases where participants have been safely dosed at the next dose level, additional dose-escalation criteria (eg, increase minimum number of participants, expand the DLT observation period, etc) for subsequent dose levels will be considered by the sponsor in consultation with participating investigators.

Participants must meet 1 of the following during the DLT observation period to be considered DLT evaluable: 1) received $\geq 80\%$ of the assigned doses of BGB-3245 and remained on study for 30 days from Cycle 1 Day 1 administration of BGB-3245; or 2) experienced a DLT during Cycle 1. Participants who fail to meet 1 of the above criteria may be replaced.

Tumor Assessments

Tumor response (antitumor efficacy) will be assessed by CT (with oral/intravenous contrast, unless contraindicated) or MRI; PET-CT is permitted as an additional assessment if indicated by the investigator. At every scheduled time point, the tumor imaging will include at minimum chest, abdomen, and pelvis, and all radiologically measurable and evaluable lesions should be assessed and documented at the Screening visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (ie, the same contrast protocol for CT/MRI scans).

- CT or MRI imaging of the brain or spinal regions (as applicable to the CNS involvement) is required during Screening for all participants and during the treatment phase in participants with suspect or known tumor lesions in the CNS.
- If a participant is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET [NaF-PET]) should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans afterwards, or if clinically indicated, TC-99m or NaF PET bone scans should be repeated when a complete response (CR) is suspected in the target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Tumor response should be assessed approximately every 8 (minus 1) weeks in the first year, then approximately every 12 (minus 1) weeks thereafter.

Tumor response will be assessed by the investigators using RECIST v1.1. The same evaluator should perform assessments, if possible, to ensure internal consistency across visits. The RECIST criteria will take priority regarding participant treatment and discontinuation decisions. Additional details are provided in [Section 7.3](#) of the protocol. For participants with ovarian cancer, tumor response will also be assessed by investigators based on Gynecological Cancer Intergroup CA-125 criteria (as detailed in [Protocol Appendix 16.7](#)).

Central Review of Tumor Assessment Scans (Phase 1b Only)

For all groups in Phase 1b, sites will submit all CT and/or MRI scans to the central imaging core laboratory for Central Imaging Review. The purpose of the Central Imaging Review is to provide an independent, unbiased, and objective review of the CT and MRI data. The Central Imaging Review will begin when deemed appropriate by the sponsor. Sites will be provided an Imaging Acquisition Manual and an Imaging Submission Manual, which describe the imaging methods and submission process that must be followed. All image data submitted to the central imaging core laboratory must be de-identified prior to submission. The participant identifiers on the image data must be consistent with all study-related documents throughout the study. See imaging manuals for details on the de-identification requirements.

Statistical Methods

Descriptive statistics will be used to summarize the demographic, disease characteristic, efficacy, and safety data.

Analysis Populations

- The Safety Population will include all participants who received at least 1 dose of study drug.
- The Efficacy Evaluable Population will include all dosed participants who have radiologically confirmed evaluable disease at baseline, and at least 1 evaluable post-baseline, radiological tumor response assessment.
- The DLT Evaluable Population will include participants who received $\geq 80\%$ of the assigned dose of BGB-3245 during the dose-escalation phase (Phase 1a) or who experienced a DLT during the dose-escalation phase (Phase 1a).
- The PK Population will include all dosed participants for whom valid BGB-3245 PK parameters can be estimated.
- The PDx Population will include all participants with valid BGB-3245 PDx sampling after treatment with BGB-3245.

Sample Size

The study plans to enroll as follows:

- Phase 1a: Approximately 28 to 60 participants for the dose escalation until MTD and/or RP2D determination.
- Phase 1b: Approximately 105 participants will be treated to achieve up to 75 evaluable participants in the 2 groups. Groups 1 and 2 will be evaluated separately. Participants who fail to meet the criteria for being evaluable will be replaced. Each group may be closed due to futility or clinical efficacy based on statistical evaluation or insufficient participant recruitment. If promising preliminary efficacy results have been observed in any of the arms after treating all planned participants (eg, higher ORR or longer PFS), more participants could be added to that arm to further assess the efficacy before moving into Phase 2/3 clinical development.

Safety Analysis

Safety will be determined by the reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, Eastern Cooperative Oncology Group, ophthalmological examination, and ECG findings will also be used in determining the safety profile.

The severity of AEs will be graded according to the NCI-CTCAE v5.0.

The incidence of AEs will be presented as the number (percentage) of participants with treatment-emergent adverse events by system organ class and preferred term by Medical Dictionary for Regulatory Activities (MedDRA). Descriptive summary statistics (ie, n, mean, standard deviation,

median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters, ECGs, and vital signs. In addition, the categorical analysis of QTc outliers (number [%] of maximum individual absolute QTc values and maximum individual QTc change from baseline) will be presented according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E14 guideline.

Efficacy Analysis

The efficacy endpoints based on response assessments using RECIST v1.1 (ie, ORR, DOR, duration of stable disease [DSD], PFS, DCR, CBR, and OS) will be summarized to evaluate the antitumor activities of BGB-3245.

In Phase 1a, investigator assessment of tumor response was performed and used for the treatment decisions.

In Phase 1b, both investigator assessment and central review will be performed, where the investigator's assessment will be used for the treatment decisions and the central review results will be collected and may be used for a retrospective analysis by the sponsor.

- ORR is defined as the proportion of participants who had confirmed CR or partial response (PR).
- DOR is defined as the time from the first determination of a confirmed objective response until the first documentation of progression or death due to any cause, whichever comes first.
- DCR is defined as the proportion of participants with best overall response (BOR) of confirmed CR, PR, or stable disease (SD).
- PFS is defined as the time from the date of the first administration of study drug to the date of the first documentation of disease progression or death due to any cause, whichever occurs first.
- CBR is defined as the proportion of participants with BOR of confirmed CR, PR, or SD lasting ≥ 24 weeks.
- OS is defined as the time from the date of first administration of study drug to the date of death due to any cause.

The ORR, DCR, and CBR will be summarized with the 2-sided exact (Clopper-Pearson) 95% confidence interval. The time-to-event endpoints, including PFS, DOR, DSD, and OS will be analyzed by Kaplan-Meier methods. Statistical methods will be described in detail in the statistical analysis plan.

Pharmacokinetic Analysis

BGB-3245 PK variables (ie, AUC_{last} , $AUC_{0-\infty}$, C_{max} , T_{max} , $t_{1/2}$, apparent clearance, and V_z/F) were planned to be calculated after single dosing in Phase 1a, if sufficient data were available. In addition, $AUC_{last,ss}$, AUC_{tau} , $C_{max,ss}$, and $T_{max,ss}$ were planned to be calculated at steady state in Phase 1a, if sufficient data were available.

The PK parameters were to be calculated as appropriate using noncompartmental methods. BGB-3245 plasma concentration data and PK parameters will be tabulated and summarized descriptively.

Other Exploratory Analyses

Summary statistics will be provided for predictive and PDx biomarkers, including but not limited to mutation, transcription, and phosphorylation profiles of mitogen-activated protein kinase pathway signaling in biopsies and blood. Depending on the data available, the analysis for biomarkers will be descriptive in nature.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
A/G	albumin/globulin ratio
AE	adverse event
AESI	adverse event of special interest
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARAF	A-Raf proto-oncogene serine/threonine kinase
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
AUC _{0-8h}	area under the plasma concentration time curve from 0 to 8 hours
AUC _{0-24h}	area under the plasma concentration time curve from 0 to 24 hours
AUC _{0-∞}	area under the plasma concentration time curve from zero to infinity (Day 1 only)
AUC _{last}	area under the plasma concentration time curve from zero to the last measurable concentration
AUC _{last,ss}	area under the plasma concentration time curve from zero to the last measurable concentration at steady state
AUC _{tau}	area under the concentration time curve for the dosing interval at steady state
BIL	bilirubin (in urine)
BLO	blood occult (in urine)
BOR	best overall response
BRAF	v-RAF murine sarcoma viral oncogene homolog B
Ca	calcium
CBR	clinical benefit rate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C _{max}	maximum observed plasma concentration
C _{max, ss}	maximum observed plasma concentration at steady state
CNS	central nervous system

Abbreviation	Definition
CPK	creatine phosphokinase
CR	complete response
CRAF	Raf-1 proto-oncogene, serine/threonine kinase
CRC	colorectal cancer
CRE	creatinine
CSR	clinical study report
CT	computed tomography
C _{trough}	trough plasma concentration
CV	coefficient of variation
CYP	cytochrome P450
DCR	disease control rate
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DSD	duration of stable disease
DU	dose de-escalate, unacceptable
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	End-of-Treatment
ERK	extracellular signal regulated kinase
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose PET
FIH	first-in-human
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GLU	glucose (in urine)

Abbreviation	Definition
GMCSF	granulocyte/macrophage colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-à-go-go related genes
HGB	hemoglobin
HIV	human immunodeficiency virus
HRAS	Harvey rat sarcoma virus oncogene
IB	Investigator's Brochure
IC ₅₀	the concentration of an inhibitor where the response (or binding) is reduced by half
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IOP	Intraocular pressure
IRT	Interactive Response Technology
K	potassium
KRAS	Kirsten rat sarcoma virus oncogene
LFT	liver function test
LVEF	left ventricular ejection fraction
LYMP	lymphocytes
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
MONO	monocyte
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Definition
mTPI-2	modified toxicity probability interval-2
N, n	number
NaF-PET	sodium fluoride PET
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NEUT	neutrophil(s)
NF1	neurofibromin 1
NOAEL	no-observed-adverse-effect level
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small cell lung carcinoma
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
P	phosphorus
PD	progressive disease
PDx	pharmacodynamic(s)
PDX	patient-derived xenograft
pERK	phosphorylated-ERK
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PLT	platelets
PR	partial response
PRO	protein (in urine)
PT	preferred term
QD	once daily
QTcF	corrected QT interval by Fridericia's formula
RAF	rapidly accelerated fibrosarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RET	reticulocytes

Abbreviation	Definition
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
S _{cr}	serum creatinine
SD	stable disease
SMC	Safety Monitoring Committee
SOC	system organ class
STD 10	1/10 the severely toxic dose in 10% of the animals
SUSAR	suspected unexpected serious adverse reaction
t _½	elimination half-life
T _{max}	time to maximum observed plasma concentration [defined as the time at which the maximum concentration is observed within the given dosing interval]
TC-99m	Technetium-99m
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TG	triglycerides
TP	total protein
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
V _d	volume of distribution
V _z /F	apparent volume of distribution
WHO	World Health Organization

1. INTRODUCTION AND RATIONALE

1.1. Introduction

The v-RAF murine sarcoma viral oncogene homolog B (BRAF) is a member of the rapidly accelerated fibrosarcoma (RAF) kinase family of mammalian cytosolic serine/threonine kinases, which transduces signals downstream of RAS via the mitogen-activated protein kinase (MAPK) pathway. The RAS–RAF–mitogen-activated protein kinase kinase (MEK)–extracellular signal regulated kinase (ERK) signaling cascade is among the most frequently mutated pathways in human cancer. Approximately 50% of melanoma patients possess a druggable hotspot V600E/lysine mutation in the BRAF protein kinase. The United States (US) Food and Drug Administration (FDA)-approved combination therapies of BRAF and MEK inhibitors are available and have provided survival benefits to patients with a BRAF V600 mutation. Non-V600 BRAF mutants are found in many cancers and are more prevalent than V600 mutations in certain tumor types. For example, between 50% and 80% of BRAF mutations in non-small cell lung carcinoma (NSCLC) and 22% to 30% in colorectal cancer (CRC) encode for non-V600 mutants. As next-generation sequencing becomes increasingly used in clinical practice, oncologists are frequently identifying non-V600 BRAF mutations in their patients' tumors but are uncertain of viable therapeutic options that could be employed for optimal treatment. From recent studies, a new classification system is emerging for BRAF mutations based on biochemical and signaling mechanisms associated with these mutants. Class I BRAF mutations affect amino acid V600 and signal as RAS-independent active monomers, Class II mutations function as RAS-independent activated dimers, and Class III mutations are kinase impaired but increase signaling through the MAPK pathway due to enhanced RAS binding and subsequent RAF-1 proto-oncogene, serine/threonine kinase (CRAF) activation. These distinct classes of BRAF mutations predict response to targeted therapies and have important implications for future drug development ([Dankner 2018](#)).

First-generation BRAF inhibitors, including vemurafenib and dabrafenib, have several limitations including:

- Development of keratoacanthomas or cutaneous squamous cell carcinomas due to increased anomalies of MAPK signaling through induction of BRAF/CRAF heterodimer in the context of mutated or activated RAS (Class III tumors)
- Development of resistance through secondary mutations in key elements of the MAPK pathway and other mechanisms leading to MAPK reactivation or alternative survival pathway
- Not effective toward RAF dimer mediated non-V600E BRAF mutations or tumors with other MAPK aberrations in the MAPK pathway including Kirsten rat sarcoma virus oncogene (KRAS)/neuroblastoma RAS viral oncogene homolog (NRAS) mutations and neurofibromin 1 (NF1) mutations.

Therefore, the development of second-generation BRAF inhibitors that can improve over the first-generation BRAF inhibitors in the above-mentioned aspects is highly desirable.

1.2. BGB-3245

BGB-3245 is a second-generation BRAF dimer inhibitor that has demonstrated potent inhibitory activity against the RAF family of serine/threonine kinases. It is a molecularly targeted therapeutic agent for the treatment of cancers with aberrations in the MAPK pathway, including BRAF mutations and KRAS/NRAS/HRAS (Harvey rat sarcoma virus oncogene) mutations as either monotherapy or in combination with other cancer therapies.

BGB-3245 is differentiated from current registered agents that target RAF kinases in the following aspects:

- BGB-3245 inhibits RAF dimers with nanomolar potency and targets non-V600E BRAF mutations and BRAF/MEK inhibitor-resistant tumors.
- BGB-3245 has reduced paradoxical increase of MAPK signaling that could lead to the development of keratoacanthomas or cutaneous squamous cell carcinomas; therefore, BGB-3245 has a lower risk for inducing secondary cancers.

Preclinical studies using biochemical, cell-based, and in vivo animal studies have suggested that BGB-3245 could offer a significant benefit to patients harboring tumors with BRAF V600E mutations (including colorectal and other nonmelanoma BRAF cancers), non-V600 BRAF mutations, and KRAS/NRAS mutation. Additional benefits include the potential to prevent or reduce drug resistance. These unique characteristics warrant further evaluation in clinical studies.

1.2.1. Pharmacology of BGB-3245

BGB-3245 is an orally administered, selective, and potent small-molecule inhibitor of RAF monomer and dimer kinases. Biochemical assays show that BGB-3245 is a pan-RAF kinase inhibitor and inhibits the catalytic activity of BRAF V600E mutant, wild-type BRAF, and CRAF kinases with sub-nM to single-digit nM IC_{50} , the concentration of an inhibitor where the response (or binding) is reduced by half. Kinase selectivity of BGB-3245 was tested against a panel of 354 human wild-type kinases at 2 μ M by Life Technologies. IC_{50} measurement revealed that IC_{50} for 5 kinases was within 10-fold of IC_{50} for BRAF V600E and IC_{50} of 23 kinases is within 10- to 50-fold of IC_{50} for BRAF V600E. Cellular assays demonstrate that BGB-3245 potently inhibits the phosphorylation of ERK protein in BRAF V600E mutant cells with IC_{50} s in the range of 6 to 16 nM. More notably, BGB-3245 inhibits the MAPK signaling in SK-MEL239 C4, a vemurafenib-resistant cell line that expresses p61 BRAF V600E dimers at the same concentrations as it inhibits pERK in SK-MEL239, the parental cell line that expresses BRAF V600E mutant monomers, suggesting that BGB-3245 inhibits RAF monomers and dimers with similar potency. Furthermore, BGB-3245 inhibits pERK in a number of KRAS mutant cell lines, with IC_{50} s in the range of 177-768 nM. Consistent with its inhibition of MAPK pathway signaling in both RAF monomer and dimer-driven cells, BGB-3245 inhibits the proliferation of tumor cells harboring not only BRAF V600E mutations but also BRAF non-V600 mutations as well as KRAS activating mutations. Details are noted in the BGB-3245 Investigator's Brochure (IB).

The antitumor activity of BGB-3245 was further demonstrated in several in vivo mouse models. Notably, among 4 models tested, vemurafenib showed effects on tumor growth only in the A375 human melanoma xenograft model, which is driven by BRAF V600E mutant monomers. In the

other 3 RAF dimer-driven tumor models, vemurafenib did not show antitumor activity. By comparison, single-agent BGB-3245 demonstrated significant antitumor activity in these RAF dimer-driven tumor models. In the intracranial K1AA1549-BRAF mouse tumor model, BGB-3245 inhibited ERK phosphorylation and significantly prolonged the survival of tumor-bearing mice. In the melanoma patient-derived xenograft (PDX) model harboring an AGK-BRAF fusion, BGB-3245 or trametinib single-agent treatment produced complete remission.

However, upon re-challenge, BGB-3245 treatment led to tumor regression, while trametinib treatment only slowed tumor growth. The CRC PDX model with a BRAF K601E mutation (Class II BRAF mutation) was insensitive to vemurafenib, cetuximab, and combination of the 2 agents. In contrast, single-agent BGB-3245 potently suppressed tumor growth. In the Calu-6 (KRAS Q61K mutant NSCLC) xenograft model, single-agent BGB-3245 led to 62.5% tumor regression. In summary, single-agent BGB-3245 has significant antitumor activity in vivo against tumor models in which the tumor growth is driven either by RAF monomer or by RAF dimer.

The in vitro hERG (human ether-à-go-go related genes) assay showed that the IC₅₀ of BGB-3245 was 7.4 μM. The conscious beagle dog cardiovascular safety pharmacology study showed that a single oral dose of BGB-3245 up to 2 mg/kg did not produce significant or toxicological effects on electrocardiogram (ECG) parameters, blood pressure, or heart rate. In rats, a single oral dose of BGB-3245 up to 10 mg/kg showed no significant effects on central nervous system (CNS) or respiratory function. In a 28-day repeat-dose toxicology study in dogs, no abnormal changes in ECG or cardiovascular histopathology were observed up to the high dose of 2 mg/kg. No changes in CNS and respiratory system function or histopathology were observed in the 28-day repeated-dose toxicity test in rats and dogs.

1.2.2. Toxicology

The nonclinical toxicological and toxicokinetic studies for BGB-3245 include single-dose toxicity tests in Sprague Dawley rats and beagle dogs, repeated toxicity and toxicokinetic tests on Days 14 and 28 for both species, and a combination of genotoxicity standard tests including bacterial back-mutation test, chromosome aberration test, and rat peripheral blood cell micronucleus test.

Because the BRAF is highly homologous across species, rats and dogs were used as the toxicological species. BGB-3245 had good bioavailability in both rats and dogs, and the metabolites were similar to those identified from a human microsome study (BGB-3245 IB). The dose of the repeated dosing study was selected based on the toxicity study results from the single dosing and 14-day repeated dosing studies for both species. Oral administration is consistent with the clinical intended route for administration.

In the toxicity studies for single dosing in rats and dogs, the maximum tolerated dose (MTD) was 30 mg/kg. In the 14-day repeated-dose toxicity in rats, the doses administered were 0, 3, 10, and 30 mg BGB-3245/kg/day. Some animals (9 of 22) in the 30 mg/kg/day group died during the experiments, and lesions were found in the brain, pituitary, liver, kidney, gastrointestinal tract, bone, bone marrow, lymph nodes, adrenal glands, spleen, and thymus, mainly as single-cell necrosis with neutrophil (NEUT) infiltration and aggregation, cell hypertrophy, or

mineralization, which are associated with clinical pathological findings. Clinical pathology changes included increases in red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), reticulocytes (RET), platelets (PLT), lymphocytes (LYMP), eosinophils, albumin (ALB), total protein (TP), albumin/globulin ratio (A/G), calcium (Ca) and potassium (K), lysine, NEUT, monocyte (MONO), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), triglyceride (TG), urea, and creatinine (CRE), as well as glucose (GLU), bilirubin (BIL), blood occult (BLO), leukocytes, and protein (PRO) found in the urine. No abnormal clinical symptoms, clinical pathology, or macroscopic lesions were observed in the 3 and 10 mg/kg/day groups.

In the 28-day repeated dosing toxicity study in rats, the doses administered were 0, 1, 3 and 10 mg/kg/day, reducing to 6 mg/kg/day. Three (3 of 23) females in the 10 mg/kg/day group were found dead or dying on Day 7 or Day 8; from Day 8, the dose for surviving animals in this group was reduced to 6 mg/kg/day. In addition to the above 3 animals, no other animals in the experiment died. Infiltration of slightly dispersed cell mixture (NEUT, macrophages, and LYMP) was observed in the meninges of the dead animals, which is considered to be the cause of death. The animals displayed dose- and time-dependent weight loss (16.5% for males and 7.8% for females) and reduced food intake during the dosing period; the NEUT showed a dose-dependent and mild increase (up to 59% and 54% for males and females, respectively); ALT was increased slightly in males and females in 10/6 mg/kg/day group (up to 64% and 39% for males and females, respectively). At the end of the experiment, there was no abnormality in the necropsy and histopathological examination, and 3 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL).

In the 14-day repeated-dose toxicity study in dogs, the doses administered were 3 mg/kg/day, 10 mg/kg/day reducing to 1 mg/kg/day, and 30 mg/kg/day. The animals in the 10 mg/kg/day and 30 mg/kg/day groups were discontinued 2 days after the administration due to severe toxic reactions; the animals in the 10 mg/kg/day group were re-administered 1 mg/kg/day from Day 12 to Day 14; the animals in the 30 mg/kg/day group were euthanized on Day 4 to Day 6 due to the dying condition; gastrointestinal bleeding was found by necropsy. Severe toxic responses were observed in the 10 and 30 mg/kg/day groups including: reduced activity, abnormal feces, proneness, fever, vomiting, salivation, significant weight loss, reduced food intake, or lack of consumption. The observed changes in clinical tests in the 30 mg/kg/day group were primarily associated with the dying status of the animals. Clinical changes in animals at the 3 and 10/1 mg/kg/day doses included: increased white blood cell count, NEUT, MONO, and/or fibrinogen; decreased RBC, HGB, HCT, RET, P (phosphorus), K, mean platelet volume, TP, ALB, A/G, GLU, and/or Ca. Smaller than normal thymus was found in the animals at all doses.

In the 28-day repeated dosing toxicity test in dogs, the dosing amounts were 0, 0.2, 0.6, and 2 mg/kg/day, and no deaths or toxicological changes were observed. Animals in the dosing period displayed transient, sporadic soft or mucoid stools; and there was a slight decrease in RET (absolute value of reticulocyte count) in the females in the 0.6 and 2 mg/kg/day groups; there was a slight decrease in P and K in all dosing groups; a slight increase in ALT occurred in male in the 2 mg/kg/day group. Histopathological changes were limited to slight to mild increases in mixed cell infiltrates around the hepatic veins in dosing animals and were not considered to be detrimental. The NOAEL was considered as 2 mg/kg/day. In the toxicity test for the 28-day

repeated dosing in rats and dogs, no visualized lesions or histopathological changes associated with drug administration were observed in the male and female reproductive organs.

No mutagenic or chromosomal cleavage toxicity was observed in the genotoxicity standard combination test (including in vitro Ames test, chromosomal aberration test, and rat peripheral blood cell micronucleus test). BGB-3245 has a low genotoxic risk at this stage of development.

In conclusion, the toxic response is dose-dependent, with notable toxicities including gastrointestinal, bone marrow, liver, and kidney toxicity presented with the symptoms of weight loss, abnormal stools (blood in the stool/diarrhea), erythrocytosis, ALT, AST, ALP, TBIL, UREA, CRE, and NEUT increase as well as urine abnormalities. In the 28-day repeated dosing toxicity studies in rats and dogs, the main changes included weight loss, mild RET reduction, mild NEUT and ALT increase; and no significant abnormalities were found in necropsy or histopathological examination; only infiltration of mixed cells (NEUT, macrophages, and LYMP) was observed in meningeal of dead rats, which was believed to be the cause of animal death. In the toxicity tests for 14 days repeated dosing in rats and dogs, under the lethal dose or MTD, clinical symptoms included weight loss and fever; clinical changes included decreases of RBC, HGB, HCT, RET, PLT, LYMP, eosinophils, ALB, TP, A/G, Ca, and K; increases of NEUT, MONO, ALT, AST, ALP, TBIL, TG, UREA, and CRE; as well as GLU, BIL, BLO, leukocytes, and PRO found in urine; histopathological examination revealed lesions in multiple organs including the brain, liver, kidney, gastrointestinal tract, bone and bone marrow, lymph nodes, spleen, thymus, adrenal glands, correlated with clinical observations, and clinicopathological examinations. Systemic area under the plasma concentration time curve (AUC) increased proportionally with dose, with no significant gender differences or drug accumulation. Based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guideline, the completed toxicology and safety assessments are adequate to support the clinical trials of BGB-3245 in patients with malignancies.

The preclinical safety evaluation results suggested that clinical trials should monitor the clinical pathology especially changes in hematology and parameters of liver and kidney functions on a regular basis in order to detect the possible myelosuppression and changes of liver and kidney functions caused by the drug. According to the toxicity test in rats and dogs, possible increase of NEUT and the corresponding clinical symptoms should be followed closely, and treatments need to be taken timely. In addition, the patient's vital signs and ECG changes also need to be followed closely in order to prevent the occurrence of infection.

Refer to the [BGB-3245 IB](#) for more detailed information on BGB-3245.

1.3. Clinical Experience

1.3.1. BGB-3245-AU-001 Enrollment Status

As of September 2022, 42 participants were evaluated in 6 dose-escalation cohorts of BGB-3245, including 5 mg once daily (QD) (n=4), 10 mg QD (n=12), 15 mg QD (n=7), 25 mg QD (n=7), 40 mg QD (n=8), and 60 mg QD (n=4). The Phase 1a portion of the study was completed.

In a review of the populations in the study, there were 31 (74%) participants had BRAF mutations and 11 (26%) with RAS mutations. Among the participants with BRAF mutations, 18 had V600E mutations, 5 had Class II mutations, and 8 had BRAF fusions. Among the participants with RAS mutations, 6 had KRAS mutations, 4 had NRAS mutations, and 1 had HRAS mutations.

The Phase 1b portion of the study is ongoing.

1.3.2. BGB-3245-AU-001 Safety Review

In a review of the 42 participants in the Phase 1a portion of the study who received at least 1 dose of BGB-3245, as of 1 September 2022, data cutoff, dose limiting toxicities were seen in 2 of 8 participants at 10 mg, 2 of 8 participants at 40 mg, and 3 of 4 participants at 60 mg. The dose of 60 mg was determined to be above the MTD; therefore, 40 mg was determined to be the MTD of BGB-3245.

In a review of the 42 participants, the most common treatment-emergent adverse events (TEAEs) were rash acneiform (38.1%), nausea (28.6%), rash maculopapular (28.6%), dyspnea (28.6%), fever (23.8%), abdominal pain (23.8%), anemia (23.8%), ALT increased (21.4%), AST increased (21.4%), platelet count decreased (19.0%), fatigue (19.0%), diarrhea (16.6%), constipation (14.3%), pruritis (11.9%), and alkaline phosphatase increased (11.9%). Most of these events were Grades 1 and 2. The most frequently reported treatment-related AEs (TRAEs) were rash acneiform (33.3%), rash maculopapular (23.8%), fever (16.6%), and platelet count decreased and ALT elevations (each 11.9%), fatigue, dyspnea, and nausea (each 9.5%). Most of these events were Grades 1 and 2. Most AEs occurred within the first 2 cycles of therapy and did not require dose modification. Twelve participants (28.6%) experienced drug-related serious adverse events (SAEs), including pyrexia (6 participants), platelet count decreased (2 participants), angioedema (2 participants), and 1 participant for each of the following events: acute kidney injury, anemia, atrial fibrillation, colitis, dermatitis acneiform, drug-induced hypersensitivity syndrome, dyspnea, ECG T wave abnormal, hypotension, pain in extremity, rash (other), rash maculo-papular, rectal haemorrhage, and rhabdomyolysis. Some participants had multiple events, but these were all recorded as separate events.

A summary of treatment-emergent adverse events (TEAEs) from the Phase 1a portion of the study are presented in the [Table 1](#). There was no clear dose-response relationship for safety across the assigned dose levels from 10 mg to 40 mg in terms of safety parameters. Although a trend of higher SAEs related to BGB-3245 (serious adverse reaction: SAR) was observed with escalating dose levels, different types of SARs were observed at all dosages, indicating no clear dose-response relationship for SARs.

Overall, the safety analysis suggested that BGB-3245 had a manageable safety profile up to 40 mg, with no clear dose-response relationship for safety.

Table 1: Summary of Treatment-Emergent Adverse Events

	5 mg N=4 n (%)	10 mg N=12 n (%)	15 mg N=7 n (%)	25 mg N=7 n (%)	40 mg N=8 n (%)	60 mg N=4 n (%)	Overall N=42 n (%)
TEAEs	4 (100)	12 (100)	7 (100)	7 (100)	8 (100)	4 (100)	42 (100)
Serious TEAEs (SAE)	2 (50.0)	8 (66.7)	5 (71.4)	3 (42.9)	4 (50.0)	4 (100)	26 (61.9)
TEAEs related to BGB-3245	0	10 (83.3)	5 (71.4)	6 (85.7)	7 (87.5)	4 (100)	32 (76.2)
SAEs related to BGB-3245 (SAR)	0	2 (16.7)	0	2 (28.6)	4 (50.0)	4 (100)	12 (28.6)
TEAEs of Grade ≥ 3 related to BGB-3245	0	3 (25.0)	0	1 (14.3)	4 (50.0)	4 (100)	12 (28.6)
TEAEs of Grade ≥ 3	2 (50.0)	9 (75.0)	5 (71.4)	3 (42.9)	4 (50.0)	4 (100)	27 (64.3)
TEAEs leading to treatment discontinuation	1 (25.0)	3 (25.0)	1 (14.3)	0	1 (12.5)	2 (50.0)	8 (19.0)
TEAEs leading to dose-reduction	0	1 (8.3)	0	0	1 (12.5)	1 (25.0)	3 (7.1)

1.3.3. BGB-3245-AU-001 Efficacy Review

As of 1 September 2022, 33 study participants were evaluable for response. The objective response rate (ORR) in the 33 participants who were efficacy evaluable was (18%) as of 1 September 2022. There was 1 complete response (CR) (at 40 mg) and 5 confirmed partial responses (PRs) (see [Table 2](#) below). The disease control rate (DCR) was 42%, with 8 additional participants with stable disease (SD) ≥ 24 weeks.

Table 2: Best Objective Response per Dose Level

Best objective response	5 mg (N=4)	10 mg (N=12)	15 mg (N=7)	25 mg (N=7)	40 mg (N=8)	60 mg (N=4)
CR	0	0	0	0	1 (13%) Melanoma BRAF V600E	0
PR	1 (25%) Mucinous ca of the appendix KRAS G12D	1 (8%) Melanoma NRAS G12S	1 (14%) Low Grade Serous Ovarian Cancer BRAF V600E	1 (14%) Melanoma NRAS Q61K*	1 (13%) Melanoma BRAF V600E	2 (50%) Endometrial cancer BRAF K601E Cholangiocarcinoma BRAF V600E*
SD	0	4 (33%)	3 (43%)	2 (29%)	2 (25%)	0
PD	1 (25%)	3 (25%)	3 (43%)	1 (14%)	2 (25%)	0
NE	2 (50%)	4 (33%)	0	3 (43%)	2 (25%)	2 (50%)

*The following participants have unconfirmed PR: melanoma NRAS Q61K at 25 mg and cholangiocarcinoma BRAF V600E at 60 mg.

In an early review of the data from Group 2 (based on raw data as of 19 January 2024), 19 participants were treated in Group 2, including 13 participants with tumors harboring BRAF Class II mutations (6 evaluable) and 6 with RAF fusions (4 evaluable). Of the 6 evaluable participants with BRAF Class II mutations, there were no responders and all 6 had SD. Of the 4 evaluable RAF fusion participants, there were 3 responders and 1 had SD. Due to this promising preliminary activity in the RAF fusion population, Group 2 will be expanded to enroll additional participants with BRAF fusions (Group 2 BRAF Fusion Expansion) to further assess clinical activity and safety in this population (see [Section 1.4.3](#), [Section 3.1.2](#), and [Section 9.1.6.1](#)).

1.3.4. BGB-3245-AU-001 Preliminary PK

Preliminary pharmacokinetic (PK) data up to Cycle 2 Day 1 for Cohort 1 (5 mg), Cohort 2 (10 mg), Cohort 3 (15 mg), Cohort 4 (25 mg), Cohort 5 (40 mg), and Cohort 6 (60 mg) were analyzed for Safety Monitoring Committee (SMC) meetings to support decisions for dose escalation. BGB-3245 appears to be rapidly absorbed after oral dosing, with a median time to maximum observed plasma concentration (T_{max}) of approximately 2 hours (range of median T_{max} of 2 to 8 hours) at Cycle 1 Day 1. Preliminary exposure data suggest that maximum observed plasma concentration (C_{max}) and area under the plasma concentration time curve from 0 to 8 hours (AUC_{0-8h}) are generally dose proportional from 5 to 40 mg at steady state. Of note, PK data for only 1 participant were evaluable at Cycle 2 Day 1 for Cohort 6; therefore, dose proportionality at steady state could not be determined for the 60-mg dose. By Cycle 2 Day 1, there was an approximately 7.4-fold average accumulation (in AUC_{0-8h}), suggestive of a long half-life. Terminal elimination could not be adequately estimated in Cycle 1 Day 1 due to sampling only up to 72 hours post-dose.

1.3.5. Comparison Between BGB-3245 and Approved BRAF Inhibitors

BGB-3245 is differentiated preclinically from current registered agents that target RAF kinases in the following aspects:

- BGB-3245 inhibits RAF dimers with nanomolar potency and shows antitumor activities in non-V600E BRAF and BRAF/MEK inhibitor-resistant tumors in preclinical models.
- BGB-3245 has reduced paradoxical increase of MAPK signaling that could lead to the development of keratoacanthomas or cutaneous squamous cell carcinomas; therefore, BGB-3245 has a lower risk for inducing secondary cancers.

1.4. Study Rationale

1.4.1. Rationale for BGB-3245 as a Monotherapy

BRAF is a member of the RAF kinase family of mammalian cytosolic serine/threonine kinases, which transduces signals downstream of RAS via the MAPK pathway. The RAS-RAF-MAPK-ERK kinase signaling cascade is among the most frequently mutated pathways in human cancer. Approximately 50% of melanoma patients possess a druggable hotspot V600E/K mutation in the BRAF protein kinase ([Dankner 2018](#)).

The first-generation BRAF targeting therapies (eg vemurafenib, dabrafenib) have been approved by the US FDA as single agents and in combinations for the treatment of melanoma ([Chapman 2011](#), [Hauschild 2012](#)). However, resistance to monotherapy with the first-generation BRAF inhibitors developed quickly in most participants, with a progression-free survival (PFS) of less than 6 months for these agents ([Chapman 2011](#), [Hauschild 2012](#)). Translational research ([Long 2014](#)) highlighted MAPK reactivation as a major resistance mechanism. First-generation BRAF V600E inhibitors, including vemurafenib and dabrafenib, have several limitations including:

- Development of resistance through secondary mutations in key elements of the MAPK pathway and other mechanisms leading to MAPK reactivation or alternative survival pathways.
- Development of keratoacanthomas or cutaneous squamous cell carcinomas due to increased activation of MAPK signaling through induction of BRAF/CRAF heterodimers; and
- Not effective toward Class II/III BRAF mutations, BRAF fusions, or tumors with other MAPK aberrations in the MAPK pathway including KRAS/NRAS mutations and NF1 mutations.

A pan-RAF dimer inhibitor like BGB-3245 can improve over the first-generation BRAF inhibitors in the above-mentioned aspects. BGB-3245 is differentiated from first-generation BRAF inhibitors due to its ability to inhibit monomer and dimer RAF proteins. BGB-3245 potently inhibits the growth of a variety of RAF and RAS mutant cell lines. In addition, BGB-3245 is highly active against a variety of clinically relevant RAF mutations in vivo, including the BRAF AGK fusion PDX model, the V600E/L514V xenograft model that is resistant to dabrafenib, and the BRAF Class II CRC xenograft model that is insensitive to

epidermal growth factor receptor (EGFR) inhibitors. Therefore, the clinical evaluation of this new chemical entity as monotherapy in a first-in-human (FIH) study in participants with advanced refractory solid tumors is appropriate.

1.4.2. Rationale for Selection of BGB-3245 Starting Dose

1.4.2.1. Compartmental Pharmacokinetic Model

BGB-3245 has good oral bioavailability in rats and dogs, ranging from 18.4% to 74.8% in rats and 68.6% to 112% in dogs. This is consistent with high permeability of BGB-3245 in Caco2 monolayer assay. The elimination half-life ranged from 1.7 to 3.2 hours in rats and 12 to 28 hours in dogs after oral administrations. Clearance was low in both rats (3.5 mL/kg/min) and dogs (0.861 mL/kg/min). Volume of distribution at steady-state was below 1.2 L/kg in both rats and dogs. The kinetics was linear over the dose range of 0.5 mg/kg to 5 mg/kg in female rats (more than dose proportional exposure was observed in male rats) and 0.2 mg/kg to 2 mg/kg in dogs. There was no accumulation of BGB-3245 following multiple oral dosing in either species. No significant gender differences in exposure were found in dogs. BGB-3245 was highly bound to plasma protein with plasma protein binding, ranging from 97.8% to 99.4% independent of concentration in mice, rats, dogs, monkeys, and humans. In rats, dogs, and humans, the blood-to-plasma ratio for BGB-3245 ranged from 0.468 to 0.688 independent of the drug concentration, suggesting BGB-3245 has a partitioning preference in plasma.

1.4.2.1.1. Interspecies Pharmacokinetic Prediction

Five different prediction methods, including the well-stirred in vitro-in vivo scaling model, simple allometric scaling model, Fu-corrected-intercept-method, 2-species rat-dog allometric method, and liver blood flow method with plasma binding correction, were used for clearance prediction. The predicted human clearance (CL) was 0.90 mL/min/kg, and the predicted human apparent volume of distribution (V_d) was 0.76 L/kg. If BGB-3245 follows simple single-exponential PK (1 compartment model) in humans, then these predictions of clearance and V_d estimate a human terminal half-life of approximately 10 hours. However, the terminal elimination half-life may be longer if BGB-3245 exhibits multiple compartment PK. Thus, BGB-3245 is very likely to exhibit a human half-life suitable for QD dosing.

The predicted AUCs at 5, 10, 20, 40 and 60 mg for a 60-kg participant were calculated using equation predicted AUC = targeted Dose $\times$ F/CL. By comparison, AUC_{0-24h} and free AUC_{0-24h} after a single dose of NOAEL (3 mg/kg/day) in rats and a single dose of NOAEL (2 mg/kg/day) in dogs were 15700 to 19300 ng $\times$ h/mL and 14500-22600 ng $\times$ h/mL, respectively, all of which are much higher than the predicted AUC at the human starting dose. The predicted safety margins for the recommended FIH doses are listed in [Table 3](#). This ensures an adequate safety margin for the FIH clinical study.

Table 3: Predicted AUC and Safety Margins for Oral Administration of Different Doses of BGB-3245 in a 60 kg Participant

Dose (mg)	Predicted AUC _{0-24h} (ng × h/mL)	Safety Margins	
		Relative to Rat	Relative to Dog
5	1014	15.5	14.3
10	2029	7.7	7.1
20	4058	3.9	3.6
40	8115	1.9	1.8
60	12173	1.3	1.2

AUC=area under the curve

Note: To be conservative, safety margins relative to the observed total AUC_{0-24h} in rat and dog are based on the lower end of AUC, 15700 ng × h/mL for rat and 14500 ng × h/mL in dog.

1.4.2.2. Recommendation of the First-in-Human Dose of BGB-3245

A common approach for many small molecules is to set a FIH starting dose at 1/10 the severely toxic dose in 10% of the animals (STD 10) in rodents. If the non-rodent is the most appropriate species, then 1/6 the highest non-severely toxic dose is considered an appropriate starting dose, based on ICH S9. In the 28-day repeat-dose study in rats and dogs, severe toxicity was noted in 6% (3/46) of rats at 6 mg/kg while the NOAEL was 3 mg/kg and 2 mg/kg in rats and dogs, respectively. Therefore, 6 mg/kg in rats and 2 mg/kg in dogs, were used for FIH dose calculation.

- The conversion factor based on body surface area is 0.16 from rats to humans (assuming the body weight is 60 kg). The human equivalent dose (HED) is 0.96 mg/kg (6×0.16). The HED per day is 57.6 mg (0.96×60). The STD 10 in rats is 5.76 mg ($57.6 \times 1/10$).
- The conversion factor based on body surface area is 0.54 from dogs to humans (assuming the body weight is 60 kg). The HED is 1.1 mg/kg (2×0.54). The HED per day is 66 mg (1.1×60). 1/6th the NOAEL in dogs is 11 mg ($66 \times 1/6$).
- Because the FIH dose supported by the rat STD 10 is lower than the FIH dose supported by the dog NOAEL (5.76 mg versus 11 mg), the lower dose based on the rat STD 10 was selected for the FIH dose (5 mg).

Therefore, 5 mg QD can be justified to be the safe FIH dose in the Phase I clinical trial.

1.4.2.3. Rationale for Use of Brimarafenib (BGB-3245)

It has been shown that enhanced RAF dimerization driven by oncogenic RAS mutations or upregulation of upstream receptors leads to intrinsic or acquired resistance to RAF inhibitors (Lito 2013, Nazarian 2010). In addition, increased RAF dimerization caused by CRAF overexpression (Holderfield 2014, Lito 2013), BRAF amplification (Shi 2012), and BRAF V600E splice variants (Poulikakos 2011) also led to resistance to first generation RAF inhibitors. Preclinical studies of BGB-3245 showed that this RAF dimer inhibitor has potential in treating cancers with resistance involving RAF dimerization.

Preclinical evaluation of BGB-3245 has demonstrated that as a RAF dimer inhibitor with nanomolar potency, BGB-3245 differentiates from the first generation BRAF inhibitors and shows anticancer activity in tumor models not only in those that harbor BRAF V600 mutations, but also in those that harbor non-V600 BRAF mutations, including BRAF fusions, and KRAS/NRAS mutations. In the Phase 1a portion of this study, early signs of activity were seen in participants with BRAF V600 melanoma who were previously treated with BRAF/MEK inhibitors, NRAS mutated melanoma, BRAF K601E/PIK3CA endometrial cancer, BRAF V600E low grade serous ovarian cancer, and KRAS G12D mutated appendiceal cancer.

The Phase 1a portion of the study included evaluations of doses of BGB-3245 from 5 mg to 60 mg as described in [Section 1.3](#). Preliminary activity was seen across dose levels in participants with malignancies harboring MAPK alterations, including participants with tumors harboring BRAF V600 mutations who had disease progression on a prior BRAF inhibitor with or without MEK inhibitor, participants with BRAF Class II mutation, and participants with BRAF fusions ([Figure 1](#)).

Given these data and the incidence and prevalence of participants with advanced solid tumors harboring the non-V600 BRAF mutations, it would be appropriate to evaluate the novel RAF dimer inhibitor BGB-3245 in these populations during the Phase 1b part of this study.

1.4.3. Rationale for the Phase 1b Dose Expansion Cohorts

As described in the previous section, second-generation pan-RAF dimer inhibitors could offer significant potential for improved clinical benefit in participants with refractory advanced cancers driven by MAPK pathway aberrations. As next-generation sequencing becomes increasingly used in clinical practice, oncologists are frequently identifying non-V600 BRAF mutations in their patient's tumors, but viable targeted therapeutic options that could be employed for optimal treatment are lacking. Non-V600 BRAF mutants have been identified in many cancers and are more prevalent than V600 mutations in certain tumor types. For example, between 50% to 80% of BRAF mutations in NSCLC and 22% to 30% in CRC encode non-V600 mutants, respectively.

A new classification system is emerging for BRAF mutations based on biochemical and signaling mechanisms associated with these mutants. Class I BRAF mutations, as exemplified by V600E, signal as RAS-independent monomers. Class II BRAF mutations function as RAS--independent activated dimers and Class III BRAF mutations are kinase impaired but increase signaling through the MAPK pathway due to enhanced RAS binding and subsequent CRAF activation. These 3 distinct classes of BRAF mutations could predict response to targeted therapies and have important implications for future drug development ([Dankner 2018](#)).

1.4.3.1. Group 1: Participants With Tumor Types Other Than CRC That Harbor BRAF V600 Mutations Who Have Been Treated and Progressed on Prior BRAF and/or MEK Inhibition

Current management of patients with solid tumors that harbor BRAF V600 mutations, particularly for the most common tumor type, melanoma, has changed as a result of recent clinical trials. In the DREAMseq-ECOG-ACRIN EA6134 trial, a 2-arm, 2-step, open-label Phase 3 trial, initial treatment or treatment sequence that yielded the best efficacy was evaluated in

participants with BRAF V600 mutant metastatic melanoma. The study demonstrated that the sequence of first-line use of checkpoint inhibitors nivolumab/ipilimumab followed by BRAF/MEK inhibitors dabrafenib/trametinib led to an improved median PFS and 2-year OS when compared to the treatment of dabrafenib/trametinib followed by nivolumab/ipilimumab ([Atkins 2023](#)). This data supported the use of BRAF ± MEK inhibitors as a later line of therapy following initial treatment with checkpoint inhibitors.

In the National Comprehensive Cancer Network (NCCN) Guidelines for the management of cutaneous melanoma ([NCCN Guidelines version 2.2024](#)), patients should receive immune checkpoint inhibitor therapy as 1L management for advanced or metastatic melanoma. The recommended therapies are nivolumab + ipilimumab, nivolumab + relatlimab, or anti-PD-1 monotherapy as a result of the above trial. For patients who progress on immune checkpoint inhibitors, BRAF/MEK inhibitor combination therapy is recommended in the 2L. For patients who then progress on BRAF/MEK inhibitor use, the recommendations are to use immune therapy, either commercially available or in a clinical trial, or tumor-infiltrating lymphocyte (TIL) therapy. Rechallenge with BRAF ± MEK inhibitors is offered to patients who demonstrated a clinical benefit from prior BRAF/MEK inhibition, but the treatment interval between rechallenge is unclear. A literature review of 7 studies comprising 400 patients with BRAF V600-mutated melanoma showed that 83% of patients who had received prior immune checkpoint inhibitors followed by BRAF/MEK inhibitor therapy would receive immune checkpoint inhibitors upon progression from the BRAF/MEK inhibitors ([Priantti 2023](#)). This literature review also noted that the disease control rate for patients with a BRAF ± MEK free interval of ≥ 6 months was greater than in patients with a BRAF ± MEK free interval of < 6 months (68% vs. 56%; $p < 0.01$). In patients with other BRAF V600-mutated tumor types like NSCLC and thyroid cancer, the NCCN recommendations are to use 1L BRAF/MEK inhibitors followed by systemic therapy ± immune checkpoint inhibitors before a rechallenge with BRAF ± MEK inhibitors ([NCCN Guidelines v4.2024](#)).

Due to the paradigm change in the treatment of BRAF V600-mutated tumors, this protocol will no longer require Group 1 participants to have had a prior BRAF and/or MEK inhibitor within 90-days prior to starting brimarafenib (BGB-3245).

1.4.3.2. Group 2: Participants with Advanced Solid Tumors Harboring a BRAF Class II or Fusion Mutation

BRAF Class II mutations and BRAF fusions have been more frequently identified in cancers due to the use of next-generation sequencing ([Owsley 2021](#)). BRAF Class II mutations have been reported in up to 17% of all non-V600 BRAF mutations ([Owsley 2021](#)). BRAF Class II mutations activate ERK signaling and are RAS independent while maintaining an intermediate to high kinase activity ([Kazandjian 2024](#), [Rustgi 2024](#), [Danker 2018](#)).

BRAF fusions have gained increasing interest due to improvements in identifying fusions through the use of next-generation sequencing, as noted in both the AACR GENIE data set and The Cancer Genome Atlas ([Kazandjian 2024](#), [Delzenne 2024](#)). BRAF fusions are a novel subset of the genomic alterations of the BRAF gene with the biological characteristics similar to the Class II BRAF mutations, but with a lower burden of co-mutations within the MAPK pathway (~2% with NF1 and ~2% with RAS in BRAF fusions as compared to 24% in NF1 and 30% with

RAS in BRAF Class II mutations) (Kazandjian 2024). This causes BRAF fusions to act similarly to BRAF Class I mutations (especially in melanoma and NSCLC). Specifically, BRAF fusions activate downstream MAPK proteins as a result of the removal of the auto-inhibitory N-terminal moiety of BRAF while maintaining kinase function, leading to expression of oncoproteins (Yu 2022, Botton 2019). There are approximately 44 different BRAF fusions that have been identified and response to therapy has been shown to be influenced by the fusion partner, attributed to differential promotion of BRAF dimerization independent of RAS (Yu 2022, Stangl 2020, Ross 2016, Stransky 2014). BRAF fusions were detected between 0.2% and 4.3% across tumor types (Dankner 2021; Kazandjian 2024), including melanoma, NSCLC, thyroid cancer, gliomas, CRC, prostate cancer, and pancreatic cancer (Stangl 2020). Moreover, the frequency of BRAF fusions may be influenced by race, as BRAF fusions were noted to occur in Black/African American patients at 15%, Asian patients at 9%, and White patients at 4% across all cancer types, respectively. More Asian patients were noted in the AACR GENIE data set to have BRAF fusions in NSCLC (19%), the highest frequency among tumor types (Kazandjian 2024).

1.4.3.2.1. Further Exploration in Participants with Advanced Tumors Harboring a BRAF Fusion

Currently, there are no standard targeted therapy for patients with advanced tumors harboring a BRAF fusion, demonstrating a high unmet medical need for these patients. In preclinical studies using a genetically engineered intracranial KIAA549-BRAF fusion model in mice, treatment with brimarafenib significantly prolonged the survival of mice bearing the KIAA1549-BRAF orthotopic brain tumors that correlated with inhibition of phosphorylated ERK (MAPK). In contrast, vemurafenib showed almost no effect on these tumors (Yao 2019). All treatments were well tolerated, and no toxicity was recorded. In addition, brimarafenib, trametinib, or vemurafenib were assessed in a patient-derived xenograft of melanoma with an AGK-BRAF fusion. Treatment with brimarafenib or trametinib, led to complete tumor regression by Day 40 in all mice, while vemurafenib had no effect on tumor growth. To assess tumor regrowth after treatment removal, drug administration was stopped on study Day 76, with tumors in both the brimarafenib and trametinib treatment groups showing tumor rebound on study Day 116. Of note, when treatment with brimarafenib and trametinib resumed on Day 120 only brimarafenib treatment led to tumor regression while trametinib treatment only was able to slow the rate of tumor progression (Yao 2019). All treatments were well tolerated.

Recent studies suggest patients with BRAF fusions may respond to a combination of a second-generation RAF dimer inhibitor with a MEK inhibitor. In a Phase 1b study of belvarafenib and cobimetinib, 15 participants with different solid tumors harboring BRAF fusions or indels showed an ORR of 66.7% (10 PR out of 15) with SD seen in 26.7% (4 out of 15) additional participants. This resulted in a median duration of response (DOR) of 12.0 months (95% CI: 7.43, 22.34) and a median PFS of 13.7 months. Ten of the 15 participants harbored BRAF fusions, with an ORR of 70% (7/10) and PRs were noted in participants harboring BRAF fusions with 6 unique binding partners (Kim 2023).

In addition, preliminary data from the Group 2 expansion cohort in this study showed early clinical efficacy in tumors with RAF fusions, and thus implores the further exploration of clinical efficacy and safety in additional participants with advanced solid tumors harboring a BRAF

fusion. Details of this expansion are described in the statistical analysis section ([Section 3.1.2](#) and [Section 9.1.6.1](#)).

1.4.4. BGB-3245 Dosing Rationale for the Phase 1b Portion of Study

The selection of dosages proposed in the Phase 1b expansion groups was based on the consideration of the preclinical data and preliminary clinical efficacy, safety, and tolerability of BGB-3245 observed in the Phase 1a part of the study.

Preclinical in vivo efficacy and PK/PDx of BGB-3245 was characterized in A375 (BRAF V600E) melanoma xenografts across a range of doses (1.56-6.25 mg/kg twice daily) in mice (see BGB-3245 IB). This dataset was used to establish a target efficacious exposure range to compare to clinical PK. When adjusted for plasma protein binding, mouse doses that resulted in significant tumor growth inhibition in A375 had free exposures similar to human (free) exposures of BGB-3245 at clinical doses ≥ 25 mg QD.

This together with the safety and efficacy data from the Phase 1a portion of the study suggesting similar and manageable safety profile of BGB-3245 up to 40 mg QD, and limited efficacy data to demonstrate a clear dose-efficacy relationship ([Section 1.3.2](#) and [Section 1.3.3](#)), the sponsor and the SMC determined that evaluation of both the 25 mg and 40 mg QD dose levels would allow for the collection of additional safety and efficacy data along with additional PK to support the selection of an optimized recommended Phase 2 dose (RP2D). These 2 doses will be evaluated in 20 participants per dose level in Group 1 of the Phase 1b portion of the study. This is a more homogeneous population and could allow for further assessment of the BGB-3245 dose optimization.

For Group 2, participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation, preclinical studies showed that tumor models possessing the BRAF Class II or III mutations had a wider range of proliferation inhibition IC₅₀ in response to the BGB-3245 treatment compared to the tumor models that harbor the BRAF V600E mutations with IC₅₀, ranging between 20 and 800 nM versus between 40 and 90 nM, respectively (refer to [BGB-3245 IB](#) for detailed information). These data suggest that the tumor response may be more heterogeneous in tumors that harbor the non-V600E BRAF mutations. In a review of the participant data as of 1 September 2022 data cutoff, there were 5 participants that had BRAF Class II mutations, and 8 participants had BRAF fusions of the 42 participants enrolled. Of the responses, one occurred at the 60 mg QD dose, higher than the maximum tolerated dose (see [Section 1.3.3](#), [Table 2](#)). Taking into consideration the preclinical data and the preliminary Phase 1a observations, the sponsor and the SMC believed that a dose lower than 40 mg of BGB-3245 would not be adequate to show benefit in participants with solid tumors harboring BRAF Class II mutations or BRAF fusions. The 40 mg MTD thus was proposed as the only dose to be evaluated for Group 2 expansion.

1.5. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with Good Clinical Practice (GCP) standards.

2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Phase 1a (Dose Escalation Part)

2.1.1. Primary Objectives

- To assess the safety and tolerability of BGB-3245 in participants with solid tumors.
- To determine the MTD, if any, and RP2D for BGB-3245.

2.1.2. Secondary Objectives

- To characterize the PK of BGB-3245 after single-dose and multiple-dose administration.
- To assess the preliminary antitumor activity of BGB-3245.

2.1.3. Exploratory Objectives

- To determine potential predictive biomarkers of molecular response.
- To assess potential pharmacodynamic (PDx) biomarkers of target engagement, biological activity, and mechanism of action.
- To explore mechanisms of treatment resistance in participants who fail to respond or develop resistance.

2.2. Study Objectives for Phase 1b (Dose Expansion Part)

2.2.1. Primary Objectives

- Evaluate the optimal RP2D for BGB-3245
- To determine the ORR as assessed by initial investigator review using Response Evaluation Criteria in Solid Tumors (RECIST version [v] 1.1) of BGB-3245 at the RP2D when given orally in participants with mutational selected solid tumors ([Appendix 16.6](#)).
- To further clarify the ORR as assessed by investigator review using RECIST v1.1 of BGB-3245 in participants with tumors harboring BRAF fusions

2.2.2. Secondary Objectives

- To determine the PFS; DCR as assessed by initial investigator review using RECIST v1.1; DOR; clinical benefit rate (CBR); and OS of BGB-3245 as a single agent.
- To further assess the safety and tolerability of BGB-3245.
- To further characterize the PK of BGB-3245.

2.2.3. Exploratory Objectives

- To determine potential predictive biomarkers of molecular response.
- To assess potential PDx biomarkers of target engagement, biological activity, and mechanism of action.
- To explore mechanisms of resistance in participants who fail to respond or develop resistance.

2.3. Study Endpoints for Dose Escalation Phase 1a

2.3.1. Primary Endpoints

- Safety and tolerability of BGB-3245 were assessed by the incidence of SAEs and the incidence and severity of AEs (coded to preferred term [PT] and system organ class [SOC]), physical examination, Eastern Cooperative Oncology Group (ECOG), vital signs, ECGs, ophthalmological examination, and laboratory tests.
- The MTD was determined by an SMC based on the occurrence of DLTs, safety, and tolerability. The sponsor defined the RP2D based on safety, preliminary efficacy, and other complementary data. The RP2D was to be confirmed by the SMC.

2.3.2. Secondary Endpoints

- For a single-dose profile: AUC from zero to the last measurable concentration (AUC_{last}), AUC from zero to infinity ($AUC_{0-\infty}$), C_{max} , T_{max} , elimination half-life ($t_{1/2}$), apparent clearance, and apparent volume of distribution (V_z/F), as available data allowed. In addition, $AUC_{last,ss}$, area under the concentration time curve for the dosing interval at steady state (AUC_{tau}), $C_{max,ss}$, and $T_{max,ss}$ were calculated at steady state, as available data allow.
- ORR was defined as the proportion of participants who had confirmed CR or PR.
- DOR was defined as the time from the first determination of an objective response per RECIST v1.1 until the first documentation of progression or death due to any cause, whichever occurred first.
- CBR was defined as the proportion of participants with best overall response (BOR) of confirmed CR, PR, or SD lasting ≥ 24 weeks.
- PFS was defined as the time from the date of the first administration of study drug to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first.
- Duration of SD (DSD) was defined as the time interval, in the absence of either confirmed CR or PR, between the date of the first administration of study drug and the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurred first.

2.3.3. Exploratory Endpoints

- Potential biomarkers of molecular response, including phosphorylated mitogen-activated protein kinase 1 (MAPK1), phosphorylated -ERK (pERK); mutational status of BRAF, KRAS proto-oncogene, GTPase (KRAS), NRAS proto-oncogene GTPase (NRAS), A-Raf proto-oncogene serine/threonine kinase (ARAF), NF1; BRAF or CRAF fusion, amplification of and other aberrations in, or affecting, the MAPK pathway. Refer to panel mutation testing described in the Laboratory Manual for a full list of genes.
- Identification of potential biomarkers of resistance: optional tumor biopsy samples taken at disease progression were used to identify potential biomarkers of resistance, including but not limited to expression or mutations (protein and RNA) of MAPK or parallel, redundant signaling pathways.

2.4. Study Endpoints for Dose Expansion Phase 1b

2.4.1. Primary Endpoints

- Determination of the optimal RP2D
- ORR (confirmed CR+PR) as described in [Section 2.3.2](#) above in participants with selected tumors.
- Further review the ORR (confirmed CR + PR) in up to 15 participants with tumors harboring BRAF fusion mutations.

2.4.2. Secondary Endpoints

- PFS as described above, DCR (confirmed CR, PR, or SD), DOR, CBR (confirmed CR or PR or durable SD [SD $\geq$ 24 weeks]), and DSD.
- OS is defined as the time from the date of the first administration of study drug to the date of death due to any cause.
- Safety and tolerability assessment of AEs, SAEs, physical examination, ECGs, and laboratory measurements.
- Pharmacokinetics assessment, including but not limited to, steady-state trough plasma concentration (C_{trough}).

2.4.3. Exploratory Endpoints

As described for Phase 1a ([Section 2.3.3](#)).

3. STUDY DESIGN

3.1. Summary of Study Design

This is an FIH, Phase 1a/1b (dose escalation and expansion) study of BGB-3245 in participants with tumors harboring BRAF or KRAS/NRAS/HRAS mutations that are likely to respond to a RAF dimer inhibitor.

Phase 1a consisted of a dose-escalation and dose-finding component to establish the MTD and/or RP2D and to evaluate the PK of BGB-3245. Phase 1b will consist of an expansion component to further evaluate the safety, tolerability, PK, and dose optimization of BGB-3245 at the RP2D(s) and to assess the preliminary antitumor activity of the compound in participants in each of the treatment groups.

Baseline tumor tissue is mandatory for mutation status and biomarker analysis, either from archived tumor tissue or fresh tumor biopsies. In Phase 1a, for participants who had readily accessible tumor lesions and who consented to the biopsies, an optional follow-up biopsy could have been taken after disease progression (ideally from the same tumor lesion as the baseline biopsy) for the analysis of PDx biomarkers.

For Phase 1b, fresh biopsies are optional after treatment discontinuation and require additional written consent. Additional biomarker analysis from blood might also be conducted by other assay types.

3.1.1. Phase 1a

Dose cohort size management and dose-escalation decisions were made in accordance with the modified toxicity probability interval-2 (mTPI-2) design ([Ji 2010](#)) and had to be confirmed by the SMC.

Periodic safety evaluations were performed by the SMC at the milestones defined by the mTPI-2 model, or more frequently if warranted by the treatment-emergent data. The SMC was established for the determination of the dose levels to be administered, and the dose regimen adjustments(s), during dose escalation, based on available data from the current and previous dose levels (see also [Section 10.1](#)). Evaluation of a cohort of at least 3 participants completing 1 cycle of treatment at that dose level was required prior to determining the dose level and dose regimen for the next cohort. The RP2D and dosing regimen to be used in Phase 1b were to be recommended by the sponsor and confirmed by the SMC and were to be based on all available safety, preliminary efficacy, PK, and exploratory data from Phase 1a. The sponsor, in consultation with the SMC, may evaluate dose levels and/or schedules that have not been predefined or eliminated. At the time of completion of the Phase 1a portion of this study, the RP2D and dosing regimen were not recommended. For the Phase 1b portion of the study, 2 dosing regimens are being evaluated.

The mTPI-2 used a Bayesian statistics framework and a beta-binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflected the relative difference between the toxicity rate of each dose level. The target toxicity rate for the MTD was $\phi = 0.30$. The maximum sample size was 60. The trial was planned to enroll and treat participants in minimum cohorts of 3 participants. Being a model-assisted design, mTPI-2 automatically and

appropriately tailored dose-escalation and de-escalation decisions with the acceptable toxicity probability interval of (0.25, 0.33). All the dose-escalation decisions were pre-calculated under the mTPI-2 design and presented in a 2-way table. The decision rules to “dose escalate” (E), “no change in dose” (S), “dose de-escalate” (D) or “dose de-escalate, unacceptable toxicity” (DU) are described in Table 4.

Cohorts of participants could have received doses already tested but a dose that was associated with decision “dose de-escalate, unacceptable toxicity” could not have been revisited and no additional participants should have been treated at this dose or higher doses for the remainder of the trial.

Table 4: Dose Escalation/De-Escalation Rule for the mTPI-2 Design

Sample size/dose level = 15, Target toxicity probability = 0.30, epsilon 1 =0.05, epsilon 2 =0.03

Number of DLTs	n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8	n=9	n=10	n=11	n=12	n=13	n=14	n=15
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	S	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	D	D	S	S	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	D	S	S	S	E	E	E
4				DU	DU	DU	D	D	D	D	D	D	S	S	S
5					DU	DU	DU	DU	DU	D	D	D	D	D	D
6						DU	DU	DU	DU	DU	DU	D	D	D	D
7							DU	DU	DU	DU	DU	DU	DU	D	D
8								DU	DU	DU	DU	DU	DU	DU	DU

* Column indicates the number of participants treated. Row indicates the number of participants with DLTs

* E: Escalate to the next higher dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose was never used again in the trial; S: Stay at the same dose.

The study enrolled and treated participants in minimum cohorts of 3 participants (see [Figure 1](#)). The design was described as follows:

1. Participants in the first cohort were treated at dose level 1.
2. To assign a dose to the next cohort of participants, conduct dose escalation/de-escalation according to Table 4. When using Table 4, please note the following:
 - a. “DU” means the current and higher doses from the trial are eliminated to prevent treating any future participants at these doses.
 - b. When a dose is eliminated, de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
 - c. If the current dose is the lowest dose and the rule indicates dose de-escalation (D), continue to treat the new participants at the lowest dose unless the number of

DLTs reaches the elimination boundary (ie, DU), at which point terminate the trial for safety.

- d. If the current dose is the highest dose, which may be higher than the predefined dose level of 60 mg, and the rule indicates dose escalation, treat the new participants at the highest dose (or the dose that is recommended by SMC).
3. Repeat step 2 until the maximum sample size of 60 is reached or stop the trial if the number of participants treated at the current dose reaches 15.

Due to binomial data variability in small samples, DLTs could have been observed in lower dose levels by chance even when the true probability (DLT) was fairly low. This could have resulted in the estimated posterior DLT rate to exceed the targeted very early in the trial, triggering an early stop when very few participants (eg, 3) had been treated. To prevent stopping the trial prematurely in such cases, a dose de-escalation option with a lower dose of 5 mg or current dose level could have been added to the dose grid.

The operating characteristics of the mTPI-2 design were described in the statistical analysis plan (SAP) for this study.

Estimating the MTD and RP2D:

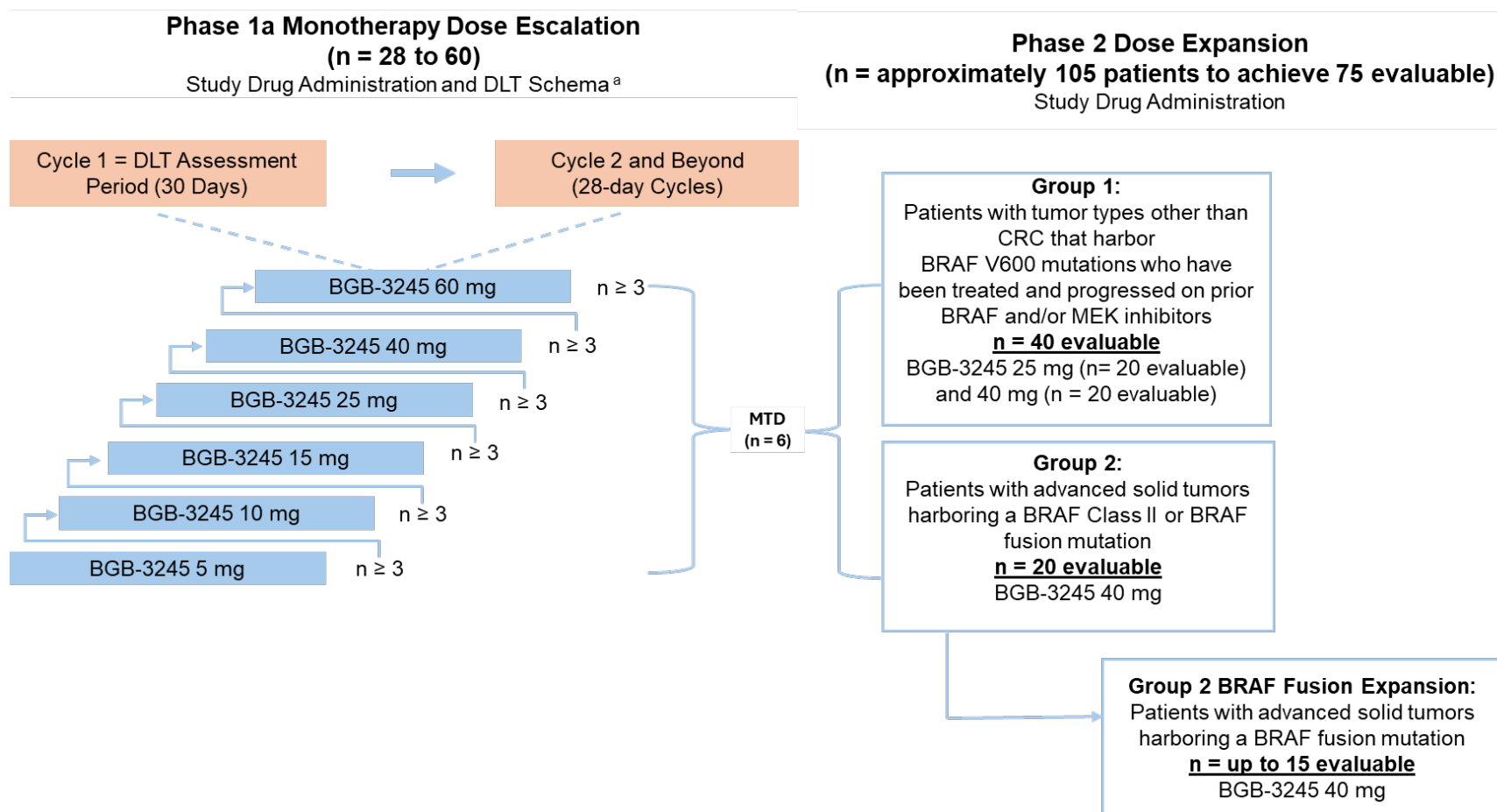
An MTD was identified at 40 mg QD, as DLTs may not be frequently observed after administration of this investigational product. The study continued accruing until 1 of the 3 stopping conditions below was triggered.

MTD and/or RP2D has been identified with sufficient accuracy: at least 6 to 12 participants had been treated on a dose that was currently estimated to be the MTD and/or RP2D; or

1. All doses explored appeared to be overly toxic
2. The maximum number of participants reached 60
3. The highest planned dose was reached and there were no more doses to test

Figure 1: Schema for Study BGB-3245-AU-001

Trial Design



Abbreviations: BRAF, v-RAF murine sarcoma viral oncogene homolog B; CRC, colorectal cancer; DLT, dose-limiting toxicity; MEK, mitogen-activated protein kinase kinase; MTD, maximum tolerated dose.

^a Dose could have been modified by 5-mg increments as deemed appropriate by the investigator.

The starting dose was 5 mg/day (5 mg QD). The 30-day initial treatment cycle (Cycle 1) of each dose level cohort consisted of a single administration of BGB-3245 on Day 1, followed by a 2-day treatment-free period (Days 2 and 3) and a 27-day period of repeated drug administration (Days 4 to 30).

3.1.2. Phase 1b

Phase 1b is a multicenter, open-label, parallel-group, dose expansion study. Phase 1b of the study will investigate the study drug dose(s) to examine the potential efficacy as well as safety and tolerability of BGB-3245 in several solid tumor indications. The following treatment groups may be considered for the dose expansion cohort:

- Group 1: Participants with tumor types other than CRC that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition (n=40 evaluable participants).
 - Participants will be randomized via Interactive Response Technology (IRT) to receive either 25 mg QD or 40 mg QD dose of BGB-3245 for a total of 20 participants evaluable for each dose level. The RP2D will be determined based on the safety, efficacy, tolerability, and the PK data obtained from participants treated with the 2 dose levels.
- Group 2: Participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation (n=20 evaluable participants).
 - Examples of Class II mutations include P367L/S, G464V/E, G469V/S/R/I/A/T170delinsAK, L485W/F, N486_A489delinsK, N486_P490del, L525R, E586K, L597V/S/R/Q/P/K, A598V/T599insV, T599I/dup/V600insT, T599I/K, T599TT/TS, V600_K601D/E/N, V600_K601del, V600_K602delinsDT, V600_W604delinsDQTDG, K601_S602delinsNT, K601E/N/T, BRAF kinase duplication. Additional Class II mutations considered upon medical monitor approval.
 - Participants in Group 2 will be treated with 40 mg QD dose of BGB-3245.
 - Treatment will be managed via the IRT system.
- Group 2 BRAF Fusion Expansion: Participants with advanced solid tumors harboring a BRAF fusion mutation (up to n=15 evaluable participants).
 - Participants in Group 2 will be treated with 40 mg QD dose of BGB-3245
 - Treatment will be managed via the IRT system.

Group 1 or participants with BRAF V600 mutated cancers who have progressed following prior BRAF ± MEK inhibitors will be evaluated using 25 mg and 40 mg QD, to confirm the RP2D in a more homogeneous population.

Definition of an evaluable participant in Phase 1b and details of the statistical assessment are provided in [Section 9.1.6](#).

3.1.3. Phase 1a and Phase 1b

During the treatment period in both parts of the study, participants will be monitored for safety, tolerability, and efficacy throughout the study from the day of first administration study drug up to 30 (+ 7) days after the last administration of study drug.

Participants were enrolled into the Phase 1a (dose escalation) component of the study in 6 dosing cohorts to evaluate the MTD and potential RP2D.

Tumor response will be assessed by investigators based on RECIST v1.1. For participants with ovarian cancer, tumor response will also be assessed by investigators based on Gynecological Cancer Intergroup (GCIG) CA-125 criteria ([Appendix 16.7](#)). The RECIST criteria will take priority regarding participant treatment and discontinuation decisions.

3.2. Study Periods, Visits, Follow-Up, or Discontinuation

Both Phase 1a and Phase 1b portions of this study consist of 3 periods. See [Section 7](#) and [Appendix 16.1](#) for study procedures to be conducted in each period.

3.2.1. Screening Period

Screening evaluations will be performed within 28 days between the date of signing the informed consent until the first administration of study drug. Participants who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure (refer to [Appendix 16.1](#) for details). However, results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to enrollment may be used for the purposes of screening rather than repeating such tests, unless otherwise indicated.

Screening evaluations may be repeated as needed within the Screening Period; however, screening tumor assessments should not be repeated unless clinically indicated. The investigator is to assess participant eligibility according to the latest screening assessment results.

Rescreening under limited conditions may be allowed after consultation with the medical monitor or designee (eg, when a participant's laboratory result narrowly miss laboratory criterion and it is correctable and not due to rapidly deteriorating condition or progressive disease [PD]).

Rescreening is allowed only once upon approval by the medical monitor or designee. If a participant is re-screened, a new signed written ICF will be required, and the participant will receive a new ID number. For those participants who are re-screened, all screening procedures per protocol should be repeated within 28 days between the re-consent and the new treatment start date.

Baseline tumor tissue is mandatory for mutation status and biomarker analysis, either from archived tumor tissue or fresh tumor biopsies.

3.2.2. Enrollment

Prior to enrollment, the investigator is responsible for assessing and confirming that each participant meets all inclusion eligibility criteria for this study and that none of the exclusion criteria apply. All results from the screening procedures and relevant medical history must be

available and reviewed by the investigator before eligibility can be determined. No eligibility waivers will be granted.

Sponsor verification of participant eligibility will be managed by way of source data verification in accordance with ICH E6.

The medical monitor will support the investigator and/or site staff by answering any queries or questions relating to protocol eligibility criteria.

Enrollment of participants to Phase 1b will be managed through an IRT system. The study-specific IRT Reference Manual and Pharmacy Manual will provide the contact information and further details on the use of the IRT system.

3.2.3. Treatment Period

After completing all screening activities, participants confirmed eligible, as detailed in [Section 3.2.2](#), and enrolled in the study will be treated with BGB-3245.

Cycle 1 Day 1 is the first day of study treatment. For Phase 1a, the first treatment cycle was 30 days, with a 2-day treatment-free period on Days 2 and 3. Starting with Cycle 2 in Phase 1a, treatment cycles were 28 days of continuous treatment (ie, no rest period). For Phase 1b, all treatment cycles will be 28 days of continuous BGB-3245 treatment. All participants will receive study drug until 1) disease progression; unless otherwise noted (see [Section 5.4.2.3](#) and [Section 7.3](#) for exceptions); 2) cessation of study treatment due to death, intolerance, or withdrawal of consent from the study; 3) completion of 2 years of treatment (unless the investigator's benefit-risk assessment supports continued treatment); 4) investigator's decision; or 5) the study is stopped by the sponsor for any reason. Details regarding study treatment are provided in [Section 5](#).

Study procedures of each clinic visit are outlined in [Section 7](#).

3.2.4. Unscheduled Visits

Unscheduled visits may occur any time as necessary as per investigator decision or participant's request for reasons such as additional assessment or follow-up of AEs. If PD is suspected, a tumor assessment should be performed (see [Section 7.3](#)).

3.2.5. Permanent Discontinuation of Study Treatment

Participants have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a participant from the study treatment at any time.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Participants may discontinue study treatment for reasons which include, but are not limited to, the following:

- Disease progression (see [Section 5.4.2.3](#) and [Section 7.3](#) for exceptions)
- AE(s)
- Death

- Pregnancy
- Major protocol deviations
- Participant withdrew consent for study treatment
- Start of other anticancer therapy

Every effort must be made to encourage the participant to complete their End-of-Treatment (EOT) visit and appropriate safety follow-ups.

3.2.6. Participant Discontinuation From the Study (End of Study for an Individual Participant)

Participants may discontinue from the study for reasons that include, but are not limited to, the following:

- Participant withdrawal of consent
- Death
- Lost to follow-up
- Completion of all study assessments (for Phase 1a participants only)

3.2.7. End-of-Treatment Visit

All participants will undergo an EOT visit within 7 days after stopping all study treatments.

A visit should be scheduled as soon as possible, but the EOT visit may occur later under specific circumstances (eg, hospitalization) and after discussion with the medical monitor. The visit at which tumor assessment showed PD may be used as the EOT visit provided that all required assessments were performed. Tumor assessment does not have to be repeated if it was performed within 8 weeks of the EOT visit or at a prior response evaluation that documented PD. Electrocardiogram does not have to be repeated if it was performed within 14 days of the EOT visit.

3.2.8. Safety Follow-up Period

Participants will return for a follow-up visit at approximately 30 (+ 7) days after last dose of the study drug or before the initiation of a new treatment, whichever comes first. If new anticancer therapy is inadvertently initiated before this safety follow-up (eg, without the knowledge of the study center team), a safety follow-up should be scheduled as soon as possible.

Adverse events (AEs) should be collected as described in [Section 7.2.7](#) and [Section 8.6](#), and may require follow up beyond 30 days.

3.2.9. Survival Follow-Up Period

Survival follow-up information will be collected only in Phase 1b (dose expansion cohorts). This information will be obtained via telephone calls, participant medical records, and/or clinic visits approximately every 3 months (± 1 week) after the EOT/Safety Follow-up visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor.

All participants (Phase 1a and Phase 1b) will be followed for disease progression, and subsequent anticancer therapy information unless a participant requests to be withdrawn from follow-up.

3.2.10. Lost to Follow-Up

If attempts to contact the participant by phone are unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The participant should be contacted by mail in a manner that provides proof of receipt by the participant. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts of contact should be documented in the participant's source documents. If a participant cannot be contacted despite all attempts, the participant will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

3.2.11. End of Study

The end of study is defined as the timepoint when the final data for a clinical study were collected, which is after final visit/follow-up has occurred for the last study participant.

However, the sponsor has the right to terminate this study at any time. Reasons for terminating the study early include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants
- Overall participant enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued participants must be seen for an EOT visit and Safety Follow-up visit as described in [Section 3.2.7](#) and [Section 3.2.8](#).

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participants' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

The sponsor has the right to close a site at any time. The decision will be communicated to the site in advance. Reasons for closing a site include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with GCP or applicable laws and regulations
- Study activity is complete (ie, all study-related activities have been completed and all obligations have been fulfilled)

3.3. Dose-Limiting Toxicity Definition

All toxicities or AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version (v) 5.0. The occurrence of any

of the following toxicities was considered a DLT during dose escalation if it occurred within 30 days of receiving BGB-3245 on Cycle 1 Day 1, with the exclusion of toxicities clearly related to disease progression or intercurrent illness.

Hematologic:

1. Any Grade ≥ 4 hematological toxicity
2. Grade ≥ 3 febrile neutropenia (defined as absolute neutrophil count [ANC] $< 1000/\text{mm}^3$ with a single temperature of $> 38.3^\circ\text{C}$ [101°F] or a sustained temperature of $\geq 38^\circ\text{C}$ [100.4°F] for > 1 hour)
3. Grade 3 neutropenia lasting > 7 days
4. Grade 3 thrombocytopenia with clinically significant bleeding

Nonhematologic:

1. Any death not clearly due to the underlying disease or extraneous causes and for any toxicity requiring permanent discontinuation of study drug(s)
2. Any Grade ≥ 4 nonhematologic event unless otherwise noted below
3. Grade ≥ 3 TBIL (except in participants with Gilbert's Syndrome) or transaminases (ALT or AST)
4. Confirmed occurrence of Hy's law or the US FDA's definition of potential drug-induced liver injury ([Section 8.2.6](#)) not explained by any other cause(s) (eg, viral hepatitis, exposure to other hepatotoxins), without evidence of cholestasis and include the following laboratory abnormalities:
 - Participants with AST or ALT and TBIL baseline values within the normal range who subsequently presented with AST or ALT values $\geq 3 \times$ upper limit of normal (ULN) concurrent with a TBIL value $\geq 2 \times$ ULN with no evidence of hemolysis and an ALP value $\leq 2 \times$ ULN or other findings indicating an absence of cholestasis
 - For participants with baseline ALT or AST values above the ULN, AST or ALT value $\geq 2 \times$ the baseline values should have been used in the definition mentioned above.

Note that this specific category of DLT uses ULN rather than CTCAE grade for definition.
5. Grade ≥ 3 rash that did not begin to resolve within 7 days of initiating optimal medical and supportive care
6. Grade ≥ 3 significant neurologic toxicity (eg, seizure, hallucination, confusion, or delirium)
7. Grade ≥ 3 generalized muscle weakness
8. Grade ≥ 3 creatine phosphokinase (CPK) with or without symptoms

9. Grade ≥ 3 nonhematologic treatment-related toxicity not listed above that did not resolve to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy

Clinically important or persistent toxicities that were not included above could also have been considered a DLT following review by the sponsor in consultation with investigators or following review by the SMC. Additionally, any clinically significant toxicities that occurred after the DLT observation period for a given dose level could have been taken into account regarding subsequent dose escalation and/or RP2D decisions.

The following toxicities were not considered a DLT:

- Isolated Grade 3 or Grade 4 laboratory abnormalities not listed above that had no clinical correlation and resolved to Grade ≤ 1 within 3 days of initiating optimal medical and supportive therapy
- Grade ≥ 3 nausea, vomiting, or diarrhea that resolved to Grade ≤ 1 within 3 days
- Grade ≥ 3 fatigue that resolved to Grade ≤ 1 within 5 days
- Grade ≥ 3 asymptomatic increase of lipase or amylase without pancreatitis that resolved to Grade ≤ 1 within 3 days

In such cases where participants had been safely dosed at the next dose level, additional dose-escalation criteria (eg, increase minimum number of participants, expand the DLT observation period, etc) for subsequent dose levels were considered by the sponsor in consultation with participating investigators.

Participants must have met 1 of the following during the DLT observation period to be considered DLT evaluable: 1) received $\geq 80\%$ of the assigned doses of BGB-3245 and remained on study for 30 days from Cycle 1 Day 1 administration of BGB-3245 or 2) experienced a DLT during Cycle 1. Participants who failed to meet 1 of the above criteria could have been replaced.

4. STUDY POPULATION

The specific eligibility criteria for selection of participants are provided in Section 4.1 and [Section 4.2](#). The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each participant eligible to participate in this study must meet all of the following criteria:

1. Participants have voluntarily agreed to participate by giving written informed consent and must be ≥ 18 years of age on the day of signing the ICF.
2. Participants with histologically confirmed advanced or metastatic solid tumor who had disease progression during or after systemic anticancer therapies that previously demonstrated clinical benefit (eg, improved survival) in a representative population, or are unable to receive standard therapy(ies). In addition, participants must meet the following eligibility criteria for the corresponding phase of the study:
 - a. Phase 1a: Participants with a known mutation status and tumor harboring an oncogenic mutation of the BRAF gene (the mutations of primary interest are the BRAF Class II mutation, Class III mutation, or BRAF fusion). In addition, participants with tumors harboring the mutation of the NRAS gene or the KRAS are eligible for Part 1a. For participants with KRAS mutations, tumor types of CRC and pancreatic cancer are excluded.
 - b. Phase 1b: Participants must have a known mutation status as assessed by local testing and meet 1 of the following criteria according to the group they are enrolled into:
 - i. Group 1: Participants with tumor types other than CRC that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition;
 - ii. Group 2: Participants with advanced solid tumors harboring a BRAF Class II mutation or a BRAF fusion mutation;
 - iii. Group 2 BRAF Fusion Expansion: Participants with advanced solid tumors harboring a BRAF fusion mutation.
3. Participants must provide archival tumor tissue or a fresh tumor biopsy for mutation status and biomarkers analysis. Fresh tumor biopsies are strongly recommended at Screening in participants with readily accessible tumor lesions.

Note: Local analysis of the mutational status is required for meeting inclusion criterion #2. Tumor samples will be used to confirm mutation status by central laboratory assessment (see exceptions noted in [Section 7.5](#)).
4. Participants must have radiologically measurable disease as defined per RECIST v1.1.
5. ECOG performance status of ≤ 1 at Screening.
6. Life expectancy ≥ 12 weeks at Screening.
7. Adequate hematologic and organ function as indicated by the following laboratory values prior to Cycle 1 Day 1:

- a. $\text{ANC} \geq 1500 \text{ cells}/\mu\text{L}$
 - b. Platelet count $\geq 100,000/\mu\text{L}$
 - c. Hemoglobin $\geq 8 \text{ g/dL}$
Note regarding hematologic function: Participant must not have received blood transfusion or growth factor support ≤ 14 days before the sample collection
 - d. Estimated creatinine clearance $\geq 50 \text{ mL/min}$ by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see [Appendix 16.8](#) for calculation)
 - e. $\text{TBIL} \leq 1.5 \times \text{ULN}$ (TBIL must be $\leq 3 \times \text{ULN}$ for participants with Gilbert's syndrome)
 - f. $\text{AST and ALT} \leq 3 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ for participants with liver metastases
8. Adequate cardiac function, as determined by:
 - a. Systolic blood pressure $< 160 \text{ mmHg}$ and diastolic blood pressure $< 100 \text{ mmHg}$ (Grade ≤ 2)
 - b. Left ventricular ejection fraction (LVEF) $\geq 50\%$ by echocardiogram or multiple-gated acquisition
 - c. No clinically significant ECG waveform abnormalities
 - d. Corrected QT interval by Fridericia's correction (QTcF) $\leq 470 \text{ ms}$, as determined by the mean QTcF values from the ECG assessments at screening (one triplicate).
9. Female participants are eligible to enter and participate in the study if they are of:
 - a. Nonchildbearing potential as defined in [Appendix 16.4](#)
 - b. Childbearing potential as defined in [Appendix 16.4](#), have a negative serum pregnancy test at Screening (within 7 days of the first dosing of study drug), and use contraception (as defined in [Appendix 16.4](#)) before study entry and throughout the study until 180 days after the last dose of the study drug
10. Male participants are eligible to enter and participate in the study if they are vasectomized or agree to use of contraception (as defined in [Appendix 16.4](#)) during the study treatment period and for at least 180 days after the last dose of the study drug.

4.2. Exclusion Criteria

Participants who meet any of the following criteria must be excluded from this study:

1. Female participants who are pregnant or lactating.
2. Participants receiving cancer therapy (chemotherapy or other systemic anticancer therapies, immunotherapy, radiation therapy, or surgery) at the time of Cycle 1 Day 1.
3. All participants who have received prior systemic anticancer treatment within the following time frames will be excluded:
 - a. Systemic chemotherapy within 4 weeks, or 6 weeks for nitrosourea, mitomycin C, prior to Cycle 1 Day 1; and
 - b. Biologic therapy (ie, antibodies), continuous or intermittent small-molecule therapies, or any other investigational agents within a period of 5 times the half-life of the agent or ≤ 4 weeks (whichever is shorter) prior to Cycle 1 Day 1

4. Active infection requiring systemic treatment at the start of the study treatment.
5. Any of the following cardiovascular criteria:
 - a. Current evidence of unstable angina or another form of symptomatic cardiac ischemia
 - b. Symptomatic pulmonary embolism or other clinically significant episode of thromboembolic disease ≤ 6 months before Cycle 1 Day 1
 - c. Acute myocardial infarction ≤ 6 months prior to Cycle 1 Day 1
 - d. Heart failure of New York Heart Association ([Appendix 16.5](#)) Classification III or IV ≤ 6 months prior to Cycle 1 Day 1
 - e. Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Cycle 1 Day 1
 - f. Cerebral vascular accident or Grade ≥ 2 transient ischemic attack ≤ 6 months prior to Cycle 1 Day 1
 - g. Grade ≥ 2 hypertension: that cannot be managed by standard antihypertension medications before Cycle 1 Day 1
 - h. Syncope or seizure ≤ 6 months before Cycle 1 Day 1
6. Any major surgery within 28 days prior to Cycle 1 Day 1.
7. Participants with toxicities that have not recovered to Grade ≤ 1 or stabilized, except for alopecia and those Grade 2 toxicities listed as permitted in the other eligibility criteria. Grade 2 neuropathy or isolated asymptomatic Grade 2 laboratory abnormality without clinical correlation may be acceptable at the investigator's discretion after consultation with the medical monitor.
8. Immune-related reactions such as pneumonitis, colitis, hepatitis, or myocarditis that did not resolve after discontinuation of prior checkpoint inhibitor use.
9. History or presence of gastrointestinal disease or other condition known to interfere with the absorption of drugs.
10. History of allergy or hypersensitivity to BRAF inhibitors or combination therapies including BRAF inhibitors.
11. Current evidence of symptomatic CNS metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Asymptomatic treated or asymptomatic untreated brain metastases are allowed as long as participants are clinically stable in the judgment of the investigator.
 - a. Participants must have a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain or spinal regions (as applicable to the CNS involvement) at Screening to confirm the stable status of the above CNS metastases
 - b. The neurological symptoms of the above CNS metastases must be stable without the use of steroids ≥ 14 days before the start of the study treatments
 - c. Participants must have no CNS surgery or radiation (except prophylactic cranial irradiation, where indicated) ≤ 28 days before Cycle 1 Day 1 and no stereotactic radiosurgery ≤ 14 days before Cycle 1 Day 1

12. Any active malignancy ≤ 3 years before Cycle 1 Day 1 except for the specific cancer under investigation in this study and any localized cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast).
13. Any participant with a solid organ transplant requiring antirejection medications.
14. Any unstable, preexisting major medical condition that in the opinion of the investigator contraindicates the use of a study drug, including known human immunodeficiency virus (HIV) or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
 - a. Participants who are hepatitis B surface antigen (HBsAg) positive or HCV antibody positive at Screening may be enrolled only if HBV DNA titers < 500 IU/mL or negative HCV RNA polymerase chain reaction test, respectively
 - b. Participants who have HIV infection at Screening may be enrolled only if CD4+ T-cell (CD4+) counts ≥ 350 cells/ μ L
15. Psychological, familial, sociological, or geographical conditions that are likely to interfere with compliance with the protocol.
16. Unfit for the study, in the opinion of the investigator, after medical interview, physical examination, or screening investigations.
17. Receiving any of the prohibited medications listed in [Section 6.1](#) or will require any of these medications.
18. Concurrent participation in another therapeutic clinical trial.
19. Receiving any treatment with a strong CYP3A4 inhibitor or inducer ≤ 14 days (or 5 half-lives, whichever is longer) before Cycle 1 Day 1, as outlined in [Section 6.2](#).

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

For the Phase 1a portion of the study, BGB-3245 was supplied in a capsule formulation. BGB-3245 will also be supplied in a capsule formulation in the Phase 1b portion of this study.

BGB-3245 capsule is an immediate-release oral solid formulation with strengths of 2.5 mg, 5 mg, and 10 mg. The capsule includes BGB-3245 (active pharmaceutical ingredient), hypromellose acetate succinate, mannitol, croscarmellose sodium, talc, magnesium stearate, microcrystalline cellulose, and capsule shell.

Each strength of BGB-3245 capsule is packaged in high density polyethylene bottles. The capsules are stored under conditions specified in the label.

Refer to the IRT study-specific Reference Manual (for Phase 1b) and the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the [BGB-3245 IB](#) for other details regarding BGB-3245.

5.2. Dosage, Administration, and Compliance

Participants will be required to fast for 2 hours before and after the administration of study drug on all days throughout the study, except on the days with PK assessments, when participants will be required to fast for 8 hours before and 2 hours after the administration of study drug. Water will be allowed freely. Grapefruit and grapefruit juice, Seville oranges, pomelos, exotic citrus fruits, or grapefruit hybrids are not allowed throughout the study. No other dietary restrictions will apply.

During Phase 1a, a single dose of BGB-3245 was administered orally on the morning of Day 1 of Cycle 1, followed by a 2-day treatment-free period (Days 2 and 3). During Phase 1a, regular daily (single dose) oral dosing after 2 hours fasting for each dose started on Day 4 of Cycle 1 and continued until the last dose of BGB-3245. For Phase 1b, all treatment cycles will be 28 days of continuous BGB-3245 treatment.

On days with PK assessments, study drug should be administered in the clinic in accordance with the schedule for the PK samples. Refer to [Appendix 16.1](#) for a full list of assessments that are required to be conducted prior to dosing. All safety-related assessments must be reviewed and dose modifications, if necessary, be made by the investigator or sub-investigator before study drug administration.

The remaining cycles may be completed as outpatients at the discretion of the treating investigator. At each study visit, empty drug containers will be returned to monitor compliance.

Participants will be treated for up to 2 years (unless the investigator's benefit-risk assessment supports continued treatment).

Phase 1a Planned Dose Levels (Oral, QD Dosing)

- Level 1: BGB-3245, 5 mg
- Level 2: BGB-3245, 10 mg (100% increase)

- Level 3: BGB-3245, 15 mg (50% increase)
- Level 4: BGB-3245, 25 mg (67% increase)
- Level 5: BGB-3245, 40 mg (60% increase)
- Level 6: BGB-3245, 60 mg (50% increase)
- Subsequent Dose Levels: TBD

The SMC could have recommended dose levels above or below these dose levels, and additional doses and/or dosing schedules could have been considered based on the safety, tolerability, and efficacy observed during dose escalation (eg, BGB-3245 at 80 mg QD or higher), including steps of 5 mg. An intermediate, not predefined, previously evaluated or not previously evaluated dose, or a less-frequent dosing schedule that did not exceed the MTD level (based on steady-state exposure) could have been considered if needed.

Phase 1b

The sponsor, in consultation with the SMC, determined the MTD in the Phase 1a portion of the study was 40 mg QD. To determine the most effective and safest dose of BGB-3245, 25 mg and 40 mg QD will be evaluated in Group 1 in the Phase 1b portion. This will include 20 evaluable participants per dose level. Additional safety, efficacy, PK and if applicable, biomarker data from this group could allow further determination of the RP2D. In Group 2 in the Phase 1b portion of the study, only 40 mg QD will be evaluated.

5.3. Overdose

There has been no case of overdose reported from the ongoing clinical study. For Phase 1b, any administration of study treatment greater than 40 mg QD (determined MTD) will be considered an overdose.

In a suspected overdose situation, emergency and supportive care should be initiated. Any overdose or incorrect administration of study treatment should be noted on the study treatment administration eCRF. Adverse events associated with an overdose or incorrect administration of study treatment will be recorded on the Adverse Event eCRF. If an overdose or incorrect administration of study treatment takes place, the sponsor is required to be immediately notified (within 24 hours of awareness).

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products required for the completion of this study will be provided by the sponsor. Any damaged shipments will be replaced.

Accurate records of all study drugs received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drug management.

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), participant drug dispensation records, and returned or

destroyed study drug(s). Dispensation records will document quantities received from sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with sponsor requirements. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and sponsor or its representative for destruction or return of unused study drug supplies.

The study-specific IRT Reference Manual will contain details on the use of the IRT system and drug supply management.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. Please refer to the study-specific Monitoring Plan for frequency of pharmacy visits.

5.4.1. Prophylactic Treatments Prior to Starting BGB-3245

As a class, RAF inhibitors may lead to cutaneous adverse reactions. Prophylactic treatments can be given according to Institutional or local guidelines. See [Appendix 16.9](#) for prophylactic care recommendations that should be implemented 2 weeks prior to the participant receiving first dose of BGB-3245.

5.4.2. Dose Delays and Modification for BGB-3245

Every effort should be made to administer the study drug according to the planned dose and schedule where it is safe to do so. Any study intervention dose greater than the determined MTD within a 24-hour period will be considered an overdose. In the event of significant toxicities, dosing may be delayed/modified based on the guidelines provided below. Reasons for dose delays, the supportive measures taken, and the outcome will be documented in the participant's chart and recorded in the eCRF. The tumor assessment schedule will not be altered even if the administration of study drug is delayed. AEs should be assessed as best as possible regarding their relatedness to BGB-3245. Investigators should discuss potential dose modifications with the medical monitor prior to implementation, if feasible. Regardless of discontinuation, participants should continue on study with regular follow-up as outlined in [Section 3.2.7](#) and [Section 3.2.8](#).

The study treatments may be restarted if the TEAE has reached satisfactory resolution per the guidelines in 14 days. The TEAE resolution to Grade 1 or baseline generally within 14 days before resuming therapy at current or reduced dose. Otherwise, treatment should be discontinued.

In rare instances, if a participant is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor.

Recommendation(s) for treatment modifications of toxicities related to BGB-3245 are summarized in [Table 5](#). Any toxicities related to BGB-3245 should be managed according to standard medical practice and in accordance with the dose modification in [Table 6](#).

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245

RELATED TEAE (Worst Grade by CTCAE V. 5.0)	INTERVENTION
NEUTROPENIA (ANC DECREASE)	
Grade 3 (ANC < 1.0 to $0.5 \times 10^9/L$)	- Interrupt BGB-3245 until resolution to Grade ≤ 1, then - If resolved to Grade ≤ 1 in ≤ 7 days, restart BGB-3245 at the same dose at the investigator's discretion. - If resolved to Grade ≤ 1 in > 7 days, restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15). - GCSF/GMCSF are permitted at the investigator's discretion except while the participant was evaluated for DLT declaration in Cycle 1 in the Phase 1a portion of the study. If the GCSF/GMCSF was administered due to a medical need, this must be declared in the eCRF as an AE.
Grade 4 (ANC < $0.5 \times 10^9/L$)	- Interrupt BGB-3245 until resolution to Grade ≤ 1, then - If resolved in ≤ 7 days, restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15). - If resolved to Grade ≤ 1 in > 7 days, permanently discontinue BGB-3245. - GCSF/GMCSF are permitted at the investigator's discretion except while the participant was evaluated for DLT declaration in Cycle 1 in the Phase 1a portion of the study. If the GCSF/GMCSF was administered due to medical need, this must be declared in the eCRF as an AE.
Grade 3 febrile neutropenia (ANC < $1.0 \times 10^9/L$ with a single temperature of $> 38.3^\circ C$ [$101^\circ F$] or a sustained temperature of $\geq 38^\circ C$ [$100.4^\circ F$] for more than 1 hour)	- Interrupt BGB-3245 until resolution of fever and ANC resolution to Grade ≤ 1. - After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15). - GCSF/GMCSF are permitted at the investigator's discretion except while the participant was evaluated for DLT declaration in Cycle 1 in the Phase 1a portion of the study. If the GCSF/GMCSF was administered due to a medical need, this must be declared in the eCRF as an AE.
Grade 4 febrile neutropenia (ANC and temperature criteria as listed above PLUS life-threatening signs or symptoms including septic shock, hypotension, and/or acidosis)	Permanently discontinue BGB-3245.

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued

THROMBOCYTOPENIA (PLATELET COUNT DECREASE)	
Grade 3 thrombocytopenia (Platelets < 50 to $\geq 25 \times 10^9/L$)	- Interrupt BGB-3245 until resolution to Grade ≤ 1, then - If resolved in ≤ 7 days, may restart BGB-3245 at the same dose at the investigator's discretion - If resolved in > 7 days, restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15) - Platelet transfusion is permitted at the investigator's discretion except while the participant was evaluated for DLT declaration in Cycle 1 in the Phase 1a portion of the study. If the transfusion was administered due to a medical need, this must be declared in the eCRF as an AE.
Grade 4 thrombocytopenia (Platelets < $25 \times 10^9/L$)	- Interrupt BGB-3245 until resolution to Grade ≤ 1, then - If resolved in ≤ 7 days, may restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15) at the investigator's discretion - If resolved in > 7 days, permanently discontinue BGB-3245 - Platelet transfusion is permitted at the investigator's discretion except while the participant was evaluated for DLT declaration in Cycle 1 in the Phase 1a portion of the study. If the transfusion was administered due to medical need, this must be declared in the eCRF as an AE.
OPHTHALMOLOGICAL	
Any Grade ≤ 2 event not leading to reduced visual acuity limiting instrumental ADL	- Either continue BGB-3245 at the same dose without interruption, if supported by the investigator's assessment or - Temporarily interrupt BGB-3245 until resolution to Grade ≤ 1 or baseline; thereafter, restart BGB-3245 at the same dose - Perform ophthalmological examinations at the frequency determined at investigator's discretion until resolution to Grade ≤ 1 or baseline
Any Grade 2 event leading to reduced visual acuity limiting instrumental ADL or Any Grade 3 event	- Temporarily interrupt BGB-3245 until resolution to Grade ≤ 1 or baseline - Perform ophthalmic examination at the frequency determined at investigator's discretion until resolution to Grade ≤ 1 or baseline - After resolution to Grade ≤ 1 or baseline, restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15) - Perform monthly ophthalmologic examinations during continued treatment, if deemed necessary at the investigator's discretion

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued

Any Grade 4 Ocular event	- Permanently discontinue BGB-3245 - Perform ophthalmic examination at the frequency determined at investigator's discretion until resolution to Grade ≤ 1 or baseline or until condition deemed stable by the ophthalmologist
NEUROLOGICAL	
Grade ≤ 2 seizure/convulsion, hallucination, confusion or delirium or similar events lasting 24 hours AND after ruling out other possible causes	- Interrupt BGB-3245 until resolution to Grade ≤ 1 - After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose
Any Grade ≥ 3 event	- Interrupt BGB-3245 until resolution to Grade ≤ 1 - After resolution to Grade ≤ 1, the investigator may restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15) or permanently discontinue BGB-3245, depending on the investigator's benefit-risk assessment
MUSCULOSKELETAL	
Grade ≥ 3 muscle weakness (symptomatic and interfering with self-care ADL)	- Interrupt BGB-3245 until resolution to Grade ≤ 1 - After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose
Grade ≥ 3 CPK increased	- Interrupt BGB-3245 until resolution to Grade ≤ 1 - Hydrate either orally or by IV as clinically appropriate. Monitor closely for myositis, pain, and weakness. - After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose
DERMATOLOGICAL	
Grade 1 skin rash (includes rash acneiform, rash maculopapular, and skin and subcutaneous tissue disorders – other manifestations might include pruritus, dry skin, etc)	- Continue BGB-3245 at the same dose without interruption - Consider using topical steroids, antihistamines, and antibiotics - Consider oral antibiotics if topical antibiotics are not improving the rash
Grade 2 skin rash	- Continue BGB-3245 at the same dose without interruption, if supported by the investigator's assessment or - Temporarily interrupt BGB-3245 until resolution to Grade ≤ 1 or baseline; thereafter, restart BGB-3245 at the same dose, if supported by the investigator's assessment - Consider addition of stronger topical corticosteroids, low dose oral corticosteroids, or retinoids - Perform dermatological examinations at the frequency determined at investigator's discretion until resolution to Grade ≤ 1 or baseline

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued

Grade 3 skin rash	- Temporarily interrupt BGB-3245 - Start oral corticosteroids - Perform dermatological examinations at the frequency determined at investigator's discretion until resolution to Grade ≤ 1 or baseline - After resolution to Grade ≤ 1 or baseline, either: - Restart BGB-3245 at the next lower dose (see Table 6, Table 12, Table 13, Table 14, and Table 15) IF the event did not begin to resolve within 7 days of initiating optimal medical and supportive care - or - Restart BGB-3245 at the same dose, if the event has started resolving within 7 days and if supported by the investigator's assessment of the benefit-risk ratio
Grade 4 skin rash	- Permanently discontinue BGB-3245 - Provide appropriate supportive care
HYPERSENSITIVITY REACTION	
Grade 3 Allergic reaction	- Interrupt BGB-3245 until resolution - Initiate oral corticosteroid therapy and/or antihistamine therapy - After resolution, BGB-3245 can be resumed at the next lower dose only after discussion with the medical monitor
Grade ≥ 3 Cytokine Release Syndrome	- Interrupt BGB-3245 until resolution - Initiate oral corticosteroid therapy and/or IL-6 inhibitors - After resolution, BGB-3245 can be resumed at the next lower dose only after discussion with the medical monitor
Angioedema	- Interrupt BGB-3245 until resolution - Initiate oral corticosteroid therapy and/or antihistamine therapy - After resolution, BGB-3245 can be resumed at the next lower dose only after discussion with the medical monitor
Anaphylaxis	- Permanently discontinue BGB-3245 - Provide appropriate supportive care
LVEF	
Grade 2 LVEF decrease that falls below the LLN (post-baseline LVEF of 40-49%)	- If asymptomatic, interrupt BGB-3245 until LVEF resolves to $\geq 50\%$. Perform LVEF examinations at least biweekly or more frequently at the investigator's discretion until satisfactory resolution. After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose. - If symptomatic, permanently discontinue BGB-3245

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued	
Grade 3 LVEF decrease (post-baseline LVEF of 20-39% or $\geq 20\%$ difference between the post-baseline vs. baseline LVEF)	• If asymptomatic, interrupt BGB-3245 and repeat LVEF examination in 1 week. If repeat examination shows persistent Grade 3 LVEF decrease, then permanently discontinue BGB-3245. • If repeat examination shows $\leq$ Grade 2 LVEF decrease, then apply the guideline listed above for Grade 2 LVEF decrease • If symptomatic, permanently discontinue BGB-3245
Grade 4 LVEF decrease (post-baseline LVEF $< 20\%$)	• Permanently discontinue study treatment
QTcF	
Grade 3 QTcF prolongation (absolute QTcF 500 msec or QTcF change from baseline 60 msec)	• Repeat ECG in triplicate approximately 1 hour after the initial ECG and consult with a cardiologist. The 3 ECGs must be recorded in close succession and not more than 2 minutes apart, and after at least 5 minutes of quiet supine rest. • Calculate the mean QTcF from the 3 ECGs • If the absolute QTcF is < 480 msec or QTcF change from baseline is ≤ 30 msec on repeat ECG triplicate, and the cardiologist agrees, then BGB-3245 may be restarted immediately at the same dose • If the absolute QTcF is > 480 msec to ≤ 500 msec or QTcF change from baseline is > 30 msec to ≤ 60 msec on repeat ECG triplicate, and the cardiologist confirms that the result is drug-related, then BGB-3245 should be temporarily interrupted during the follow-up by weekly repeat ECG triplicates. When the absolute QTcF is < 480 msec or QTcF change from baseline is ≤ 30 msec on repeat ECG triplicate, then BGB-3245 should be restarted at the next lower dose. • If the absolute QTcF is > 500 msec or QTcF change from baseline is > 60 msec on repeat ECG triplicate, and the cardiologist confirms that the result is drug-related, then BGB-3245 should be permanently discontinued
TOTAL BILIRUBIN INCREASE	
Note: Participants with documented Gilbert's Syndrome may be exempt at the investigator's discretion.	
Grade 2 (TBIL $> 1.5x$ to $3.0x$ ULN if baseline was normal; $> 1.5x$ to $3.0x$ baseline if baseline was abnormal)	• Interrupt BGB-3245 until resolution to baseline, then • If resolved in ≤ 7 days, restart BGB-3245 at the same dose • If resolved > 7 days, restart BGB-3245 at the next lower dose
Grade 3 (TBIL $> 3.0x$ to $10.0x$ ULN if baseline was normal; $> 3.0x$ to $10.0x$ baseline if baseline was abnormal)	• Interrupt BGB-3245 until resolution to baseline, then • If resolved in ≤ 7 days, may restart BGB-3245 at the next lower dose at the investigator's discretion • If resolved > 7 days, permanently discontinue BGB-3245

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued

Grade 4 (TBIL > 10.0x ULN if baseline was normal; > 10.0x baseline if baseline was abnormal)	Permanently discontinue BGB-3245
AST or ALT INCREASE	
Grade 3 AST or ALT increase (> 5.0x to 20.0x ULN if baseline was normal; > 5.0x to 20.0x baseline if baseline was abnormal)	- Interrupt BGB-3245 until resolution to Grade ≤ 1 (or Grade ≤ 2 if the participant has liver metastases) - After resolution to Grade ≤ 1, restart BGB-3245 at the next lower dose
Grade 4 AST or ALT increase (> 20.0x ULN if baseline was normal; > 20.0x baseline if baseline was abnormal)	Permanently discontinue BGB-3245
DILI/Hy's Law	
Potential DILI/Hy's Law (pending clinical adjudication)	- Permanently discontinue BGB-3245 - If clinical adjudication confirms DILI/Hy's Law, then report DILI as SAE
PNEUMONITIS	
Any event including nonproductive cough, dyspnea, and supplemental oxygen dependence with radiological findings of reticular markings, traction bronchiectasis, and ground-glass opacities, excluding alternative etiologies such as infections and lung metastasis.	- Interrupt BGB-3245 until resolution - Initiate oral corticosteroid therapy of 0.5-1 mg/kg/day of prednisone or equivalent with a taper over 4-6 weeks until resolution - After resolution, restart BGB-3245 at the next lower dose
Grade 4 pneumonitis or ILD	Permanently discontinue BGB-3245
ACUTE KIDNEY INJURY	
Any Grade ≥ 3 event of acute kidney injury	Permanently discontinue BGB-3245
DIARRHEA	
Grade 1-2 diarrhea	- Continue BGB-3245 at the same dose without interruption - Institute a low-fat diet - Consider addition of loperamide until diarrhea resolves for 48 hours
Grade 3 diarrhea	- Interrupt BGB-3245 until resolution - Institute a low-fat diet - Start loperamide every 2-4 hours until no bowel movements for 48 hours - Carefully monitor electrolyte and hydration status - Consider hospitalization - Restart BGB-3245 at 1 dose lower

Table 5: Recommendations for Adverse Event Management and Dose Modification for Toxicities Related to BGB-3245 continued

Grade 4 diarrhea	- Interrupt BGB-3245 until resolution - Manage the participant in the hospital - Consider restarting BGB-3245 at 1 dose lower
OTHER	
Grade ≥ 3 hematologic toxicities or clinically significant Grade 2 hematologic abnormalities that do not resolve within 72 hours after initiation of medical management.	Interrupt dosing, after resolution to Grade ≤ 1, restart study treatment at the next lower dose
Grade ≥ 3 nonhematologic toxicity that is not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade ≤ 1 or baseline, restart study treatment at the next lower dose

Abbreviations: ADL, Activities of Daily Living; ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice a day; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; DILI, drug-induced liver injury; DLT, dose-limiting toxicity; ECG, electrocardiogram; GCSF, granulocyte colony stimulating factor; GM-CSF, granulocyte/macrophage colony stimulating factor; ILD, interstitial lung disease; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; QTcF, corrected QT interval by Fridericia's formula; RVO, retinal vein occlusion; SAE, serious adverse event; TBIL, total bilirubin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

5.4.2.1. Dose Delays

Refer to [Section 5.4.2](#) and [Table 5](#) regarding AE severity, management, and corresponding dose delay recommendations.

Two occurrences of dose delays due to treatment-related AEs will be permitted. In the event of a third occurrence of a toxicity which would require dose delay, permanent discontinuation of study drug should be considered after consultation with the medical monitor or designee.

Dosing of BGB-3245 can be delayed for approximately 28 days for medical events that are not associated with toxicity related to BGB-3245.

5.4.2.2. Dose Reductions

Refer to [Section 5.4.2](#) regarding AE severity and corresponding dose reduction.

Dose reductions may not be required for AEs (eg, alopecia) that, in the opinion of the investigator, are not considered a safety risk for the participant and following discussion with the medical monitor.

If the administration of BGB-3245 is interrupted for reasons other than toxicity related to BGB-3245, then treatment with the study drug may be resumed at the same dose.

A participant may have the following dose reductions due to TEAEs as summarized in [Table 6](#).

Table 6: Dose Reduction Options

Dose at the time of the event	Reduced Dose
40 mg QD	25 mg QD
25 mg QD	15 mg QD
15 mg QD	10 mg QD
10 mg QD	5 mg QD
5 mg QD	Discontinue BGB-3245

Abbreviation: QD, once daily.

5.4.2.3. Dose Escalation (Phase 1a Only)

In Phase 1a only, the inpatient dose escalation was permitted in all participants who might have benefitted from the higher dose of BGB-3245 at the investigator's discretion, and who did not have clinically significant toxicities or symptomatic deterioration of the underlying cancer.

Inpatient dose escalation may have been implemented only after consultation with the medical monitor in the following cases.

BGB-3245 dose may have been escalated up to the highest dose level that had previously been determined to be safe per [Section 3.1.1](#) and deemed well tolerated by the SMC.

Inpatient dose escalation was not permitted in those participants who had previously undergone BGB-3245 dose reduction due to a TEAE.

In Phase 1b, dose escalation within a given participant is not allowed.

6. CONCOMITANT THERAPY

6.1. Prohibited or Restricted Concomitant Medications and Therapy

The following medications are prohibited or restricted during the study:

- Any systemic antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or other approved or investigational agents for the treatment of cancer) within 28 days or 5 half-lives (whichever is shorter) before the start of study treatments and during the treatment period until the EOT Visit.
- Transfusion of blood or platelet concentrates, granulocyte colony stimulating factor (GCSF) or granulocyte/macrophage colony stimulating factor (GMCSF) were prohibited in Cycle 1 in the Phase 1a portion of the study while the participant was evaluated for potential DLT declaration related to the respective types of toxicity. These are permitted for use in the Phase 1b portion of the study.
- Radiation therapy except for palliative (limited field) radiation therapy described below.
- Bisphosphonate treatment from the start of study treatments and during the treatment period until the EOT Visit. Participants who received bisphosphonate treatment before the start of study treatments may continue at the same dose of bisphosphonate during the study.
- Live vaccines (within 4 weeks before the start of the study treatments), including the intranasal flu vaccine and the monkeypox vaccine are prohibited.
 - Note: Injectable flu vaccine and inactivated vaccines are permitted at any time before the start of the study treatment and during the study.
- Chronic systemic or ocular glucocorticoid therapy within the 14 days before the start of study treatments and during the treatment period until the EOT Visit with the following exceptions:
 - Physiologic or stress doses of steroids, when indicated in participants with endocrine deficiencies.
 - Corticosteroids given as the premedication for blood product transfusions.
 - Corticosteroids given as the pulse treatment for an acute allergic reaction or bronchospasm.
 - Oral or intravenous corticosteroids for up to 6 consecutive days, when indicated for the management of AE (eg, Grade ≥ 3 thrombocytopenia) after consultation with the medical monitor and/or ophthalmologist.
- Antibiotic therapy for active infection within 14 days before the start of study treatments.
- Substrates of CYP2C8 or CYP2C9 with a narrow therapeutic range during the treatment period until the EOT Visit.

- Grapefruit and grapefruit juice, Seville oranges, pomelos, exotic citrus fruits, or grapefruit hybrids within 14 days before the start of study treatments and during the treatment period until the EOT Visit.
- Herbal remedies with a known potential to interfere with liver or other major organ functions (ie, hypericin) or act as strong CYP3A4 inhibitor within 14 days before the start of study treatments and during the treatment period until the EOT Visit.
- Strong CYP3A4 inhibitors and inducers are prohibited within 14 days prior to Cycle 1 Day 1 until the EOT visit.
- For the management of mild to moderate COVID-19, the use of ritonavir-boosted nirmatrelvir (PAXLOVID) is prohibited within 14 days prior to C1D1 until the EOT visit
- Alcohol or other illicit drugs from the signing of informed consent and during the study.

Palliative (limited field) radiation therapy or other focally ablative therapy is permitted provided the following criteria are met:

- The lesion being considered for palliative radiation is present at baseline and has not been selected as the target lesion for RECIST v1.1
- The procedure is clinically indicated by the investigator for pain control or prophylaxis of bone fracture
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met

Whenever possible, participants receiving palliative radiation therapy should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

6.2. Potential Interactions Between the Study Drug and Concomitant Medications

Clinical drug interaction information with BGB-3245 is not available. Based on available nonclinical metabolism data, the primary metabolic pathway for BGB-3245 involves the CYP3A isoform. Strong CYP3A4 inhibitors and inducers are prohibited within 14 days prior to C1D1 until the EOT visit. For the management of mild to moderate COVID-19, the use of ritonavir-boosted nirmatrelvir (PAXLOVID) is prohibited within 14 days prior to C1D1 until the EOT visit. Please refer to the PAXLOVID US Package Insert and Summary of Product Characteristics due to the potential risk of elevated plasma concentrations that may be associated with serious and/or life-threatening reactions.

Please refer to [Table 7](#) for examples of strong CYP3A4 inhibitors and inducers.

Table 7: Strong CYP3A4 Inhibitors and Inducers

CYP3A4	Strong Inhibitors	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir
	Strong Inducers	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Abbreviation: CYP3A4, cytochrome P450, family 3, subfamily A, member 4.

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A4 inhibition risks or contact the medical monitor of the protocol.

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [online]. Available from: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>; Accessed May 13, 2022.

BGB-3245 showed moderate inhibition potential against human CYP2C8 and CYP2C9; therefore, BGB-3245 has the potential to interfere with the metabolism of compounds which are CYP2C8 or CYP2C9 substrates. Drugs that are primarily metabolized by CYP2C8 or CYP2C9 should be used with caution when administering BGB-3245. Avoid concomitant administration of study drug with substrates of CYP2C8 or CYP2C9 with a narrow therapeutic range. Please refer to table 8 for examples of substrates of CYP2C8 and CYP2C9.

Table 8: CYP2C8 and CYP2C9 Substrates

CYP2C8 Substrates
amodiaquine, cerivastatin, paclitaxel,* repaglinide, sorafenib, torsemide
CYP2C9 Substrates
NSAIDs: diclofenac, ibuprofen, lornoxicam, meloxicam, S-naproxen, piroxicam, suprofen
Oral Hypoglycemic Agents: tolbutamide, glipizide
Angiotensin II Blockers: losartan, irbesartan
Sulfonylureas: glyburide, glibenclamide, glipizide, glimepiride, tolbutamide
Others: amitriptyline, celecoxib, fluoxetine, fluvastatin, glyburide, nateglinide, phenytoin,** rosiglitazone, tamoxifen, torsemide, valproic acid, warfarin,** zakirlukast

Abbreviation: CYP2C8, cytochrome P450, family 2, subfamily C8; CYP2C9, cytochrome P450, family 2, subfamily C9.

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP2C8 or CYP2C9 substrates or contact the medical monitor of the protocol.

*CYP2C8 substrates with narrow therapeutic range.

** CYP2C9 substrates with narrow therapeutic range.

Sources: [Flockhart 2021](#) and [FDA 2017](#).

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Screening

Screening evaluations will be performed within 28 days between the date of signing the informed consent until the first administration of study drug. Participants who agree to participate will sign the ICF prior to undergoing any screening procedure (refer to [Appendix 16.1](#) for details). However, results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to first administration of study drug may be used for the purposes of screening rather than repeating such tests, unless otherwise indicated.

Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess participant eligibility according to the latest screening assessment results. If a participant is re-screened, a new ICF will be required.

Procedures conducted at Screening visit only are described in [Section 7.1](#). For the description of other assessments that are conducted at Screening as well as throughout the study, refer to Safety Assessments ([Section 7.2](#)), Tumor and Response Evaluations ([Section 7.3](#)), PK Assessments ([Section 7.4](#)), and Biomarker Assessments ([Section 7.5](#)).

Screening evaluations may be repeated as needed within the Screening Period; however, screening tumor assessments should not be repeated unless clinically indicated. The investigator is to assess participant eligibility according to the latest screening assessment results.

Rescreening under limited conditions may be allowed after consultation with the medical monitor or designee (eg, when a participant's laboratory result narrowly miss laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD). Rescreening is allowed only once upon approval by medical monitor or designee. If a participant is re-screened, a new signed written ICF will be required, and the participant will receive a new ID number. For those participants who are re-screened, all screening procedures per protocol should be repeated within 28 days between the re-consent and the new treatment start date.

7.1.1. Demographic Data and Medical History

Demographic data will include age or date of birth, sex, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption (ie, presence or absence); and all medications (ie, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days before the first administration of study medication.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior medication therapy, including start and stop dates, best response, and reason for discontinuation.

Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Assessing Females of Childbearing Potential and Contraception

See [Appendix 16.4](#) for definitions of “Women of Childbearing Potential,” or “Women of No Childbearing Potential” as well as guidelines for contraception where applicable.

7.1.3. Hepatitis B and C Testing

Hepatitis B surface antigen, antibodies against HBsAg, hepatitis core antibody, and HCV serology will be tested at Screening. In addition, viral load assessment (HBV DNA or HCV RNA) will be done for participants with HBsAg positive or HCV antibody positive at Screening, respectively.

7.1.4. CD4 counts for Participants with Known HIV Infection

For participants who have HIV infection at Screening, ensure that the CD4+ T cell (CD4+) counts ≥ 350 cells/ μ L.

7.2. Safety Assessments

Vital signs, body weight, physical examinations, ECOG performance status, ECGs, and laboratory safety tests will be obtained and assessed at designated timepoints throughout the study (see [Appendix 16.1](#)). AEs and SAEs will be assessed throughout the study.

The continuous safety evaluation will be performed by the sponsor or designee.

All safety-related assessments must be reviewed and dose modifications, if necessary, be made by the investigator or sub-investigator before study drug administration. Note, some assessments must be conducted pre-dose and/or post-dose as noted in the footnotes of Appendix 16.1.

7.2.1. Vital Signs

Vital signs will include measurements of temperature, heart rate, pulse oximetry, and blood pressure (systolic and diastolic) after the participant has been sitting for at least 5 minutes.

7.2.2. Physical Examinations

A complete physical examination including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological (ie, investigator should assess for rash acneiform, rash maculopapular, and other skin toxicities), 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems is required to be performed at Screening. Any abnormality identified at baseline will be recorded on the Medical History eCRF with appropriate disease/condition terms.

Height (Screening only) and weight will be recorded. Where possible, the same scales are to be used for measurement of weight.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded in participant notes. New or worsened clinically significant abnormalities are to be recorded as AEs on the AE eCRF. Refer to [Section 8.3](#) regarding AE definitions and reporting and follow-up requirements.

7.2.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status ([Appendix 16.2](#)) will be assessed at the Screening visit, on Day 1 of each treatment cycle, the EOT visit, and the Safety Follow-up visit.

7.2.4. Ophthalmological Examination

Full ophthalmological examination should be performed at Screening, including the visual acuity, intraocular pressure, slit lamp examination, and retinal assessment (at the minimum dilated funduscopy and preferably also an optical coherence tomography [OCT] scan). The ophthalmological examinations during the BGB-3245 treatment period should be performed at Screening, every 8 (minus 1) weeks during the first year and every 12 (minus 1) weeks thereafter, and at the EOT visit (unless the prior ophthalmological assessment has been obtained within 4 weeks of the EOT visit). At the investigator's discretion, the retinal assessment may be omitted from the ophthalmological examination during the BGB-3245 treatment and at the EOT visit in those participants who had normal or clinically non-significant changes at the Screening retinal assessment.

If a participant experiences any visual symptoms (including blurred vision) or signs and symptoms of toxicity, an ophthalmic examination should be performed as soon as possible to address.

Additional tests will be conducted if clinically indicated. Any clinically significant findings and symptoms, including those confirmed by the ophthalmologist, must be reported as an AE.

7.2.5. Laboratory Safety Tests

Laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis) to be performed by a site's local laboratory are shown in [Appendix 16.3](#).

In addition, the following tests will be conducted in this study:

- A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first administration of study medication. Urine or serum pregnancy tests will be performed monthly during treatment and at Safety Follow-up. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug on Day 1 of each cycle.
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4).

7.2.6. Electrocardiograms

Local ECG machines will be used. For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. The investigator or designee will evaluate the overall ECG result as normal, or abnormal not clinically significant, or abnormal clinically significant. All abnormal clinically significant ECG results must be reported as AE or SAE. Paper or electronic copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

At each time point, triplicate (3 consecutive) 12-lead ECGs will be performed in close succession and not more than 2 minutes apart (total up to 4 minutes for 3 ECGs in a triplicate). The mean corrected QT interval by Fridericia's correction (QTcF) interval will be calculated as the average of the 3 QTcF values from each triplicate. The triplicate ECG should be performed after the participant has rested silently in supine or semi-recumbent position for at least 5 minutes. When coinciding with PK blood draws, ECG assessment should be performed at least 5 minutes before vital signs are collected and prior to blood draws ([Appendix 16.1](#)). Participants should rest in a semi-recumbent supine position for at least 5 minutes prior to ECG collection.

7.2.7. Adverse Events

AEs will be recorded throughout the study and graded according to NCI-CTCAE v5.0. Characterization of AEs will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in [Section 8.6](#). At the EOT, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or Grade ≤ 1 , the event is assessed by the investigator as stable, the participant is lost to follow-up, the participant withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

7.3. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to the first study treatment. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first administration of study drug may be used for the purposes of screening rather than repeating the standard of care tests. During the study, tumor imaging will be performed approximately every 8 (minus 1) weeks in the first year and approximately every 12 (minus 1) weeks thereafter. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

Tumor response (antitumor efficacy) will be assessed by CT scans (with oral/intravenous contrast, unless contraindicated) or MRI; PET-CT is permitted as an additional assessment if indicated by the investigator. At every scheduled time point, the tumor imaging will include, at minimum, the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening are required to be used throughout the study (eg, the same contrast protocol for CT/MRI scans).

- CT or MRI of the brain or spinal regions (as applicable for CNS involvement) at baseline (≤ 21 days of informed consent) is required during Screening for all participants and during the treatment phase in participants with suspect or known tumor lesions in the CNS.
- If a participant is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET [NaF-PET]) should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans afterwards, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when a CR is suspected in the target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Tumor response should be assessed approximately every 8 (minus 1) weeks in the first year, then approximately every 12 (minus 1) weeks thereafter.

Tumor response will be assessed by the investigators using RECIST v1.1. The same evaluator should perform assessments, if possible, to ensure internal consistency across visits. For participants with ovarian cancer, tumor response will also be assessed by investigators based on Gynecological Cancer Intergroup CA-125 criteria ([Appendix 16.7](#)). The RECIST criteria will take priority regarding participant treatment and discontinuation decisions.

After the first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later (≥ 4 weeks) after the first response or at the next scheduled assessment time point.

The following criteria must be met in order to treat participants with radiographic disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform participants that this practice is not considered standard in the treatment of cancer
- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records

For such participants treated through disease progression, refer to [Section 5.4.2.3](#) regarding inpatient dose escalation. The decision to continue study drug beyond initial investigator-assessed progression must be agreed to in writing with the sponsor medical monitor, then every 6 months and documented in the medical records.

Participants who discontinue study treatment early for reasons other than radiographic disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the participant begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

All participants' files and radiologic images must be available for source verification and for potential peer review.

7.3.1. Central Review of Tumor Assessment Scans (for Phase 1b Only)

For all groups in Phase 1b, sites will submit all CT and/or MRI scans to the central imaging core laboratory for Central Imaging Review. The purpose of the Central Imaging Review is to provide an independent, unbiased, and objective review of the CT and MRI data. All images should be submitted within 7 business days of scan date. Sites will be provided an Imaging Acquisition Manual and an Imaging Submission Manual, which describe the imaging methods and submission process that must be followed. All image data submitted to the central imaging core laboratory must be de-identified prior to submission. The participant identifiers on the imaging data must be consistent with all study-related documents throughout the study. See imaging manuals for details on the de-identification requirements.

7.4. Pharmacokinetic Assessments

The following assessments will be performed at a bioanalytical laboratory:

- Pharmacokinetic assay: plasma samples will be assayed for BGB-3245 (and possible major metabolites) concentration with use of a validated chromatography method.

Shipping, storage, and handling of samples for the PK assays will be managed through a central and/or bioanalytical laboratory. Instruction manuals and supply kits will be provided for all PK assessments. PK sampling time points are documented in [Table 13](#) and [Table 15](#) of [Appendix 16.1](#).

7.5. Biomarker Assessments

Shipping, storage, and handling of tumor tissues and blood samples for the assessment of biomarkers will be managed through a central laboratory. Refer to the Laboratory Manual for details of sample handling.

Participants will be selected for screening and eligibility based on known mutation status through the local molecular testing obtained from the tumor sample collected any time prior to screening, or if needed, during the screening period. The mutation result from the local molecular testing assay for both Phase 1a and Phase 1b must be confirmed by a central analysis testing assay. Confirmatory mutation testing should be performed at the central laboratory at any time during the study to support the study data analysis. When possible, the tumor sample tested locally should be the same as the sample tested centrally.

Definitive central laboratory mutation results (positive or negative) cannot be repeated. If a sample is determined to be inadequate or the result is indeterminate on central testing, an additional sample may be resubmitted to the central laboratory for retesting. If there is non-

concordance between the local and central laboratory results, or if the local result cannot be confirmed by central laboratory (eg, inadequate sample or poor sample quality), participants may continue receiving study treatment provided there is no clinical deterioration or disease progression and the participant is benefiting from study treatment, as determined by the investigator and in consultation with the sponsor medical monitor. In such cases, participants will be informed as soon as possible that their mutation status is unconfirmed with information to describe follow-up procedures and alternative treatment options.

Acceptable tumor mutations of interest for this study include the following genes: BRAF, ARAF, RAF1 (CRAF), KRAS proto-oncogene, GTPase (KRAS), NRAS proto-oncogene, GTPase (NRAS), HRAS proto-oncogene, GTPase (HRAS), NF1, mitogen-activated protein kinase 1 (MAP2K1), mitogen-activated protein kinase 2 (MAP2K2), MAPK1, EGFR, G protein subunit alpha 11 (GNA11), G protein subunit alpha q (GNAQ), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB), phosphatase and tensin homolog (PTEN), AKT serine/threonine kinase 1 (AKT1), MET proto-oncogene, receptor tyrosine kinase (MET), KIT proto-oncogene, receptor tyrosine kinase (KIT), and insulin like growth factor 1 receptor (IGF1R). Refer to panel mutation testing described in the Laboratory Manual for a full list of genes.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Fresh biopsies should be limited to readily accessible tumor lesions (ie, skin, peripheral lymph nodes, lung, liver, or internal lymph node metastases which can be readily accessed using CT guidance). Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. If performed, 3-5 tissue cylinders should be obtained that have proper size for histological examination and biomarker analysis (ie, pERK IHC; genomic profiling). A minimum of 3 cores per biopsy is required.

For participants who have readily accessible tumor lesions, and who consent to the biopsies, an optional fresh tumor biopsy will be performed at the time of discontinuation of the study drug. If possible, this biopsy will be performed within 2 to 4 hours after the administration of the last dose of BGB-3245, or as soon as possible thereafter.

In addition, blood samples will be collected from all participants for mutation profiling by next-generation sequencing within 14 days prior to Cycle 1 Day 1, and while on study approximately every 8 (minus 1) weeks in the first 12 months and approximately every 12 (minus 1) weeks thereafter through the EOT visit. Additional biomarker analysis from the blood might also be conducted by other assay types, such as RNA-Seq.

Freshly collected tumor biopsies, when available, and archival tumor tissues (tissues should either be a formalin-fixed paraffin-embedded block or approximately 15 unstained slides) will be sent to a central laboratory for immunohistochemistry assays and mutation profiling. In addition to BRAF, ARAF, RAF1, KRAS, NRAS, HRAS, NF1, MAP2K1, MAP2K2, MAPK1, EGFR, GNA11, GNAQ, PIK3CA, PIK3CB, PTEN, AKT1, MET, KIT, and IGF1R aberrations, other markers that are related to response or clinical benefit of BGB-3245 may also be evaluated. Refer to panel mutation testing described in the Laboratory Manual for a full list of genes.

Mutation status and participant responses will be analyzed together to enable potential development of companion diagnostics for participants most likely to benefit from treatment in the future.

7.6. Visit Windows

Refer to [Appendix 16.1](#) for visit windows.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date with subsequent visits conducted according to the planned schedule.

8. STUDY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Guidelines on Management of Selected Adverse Events

BGB-3245 is a study drug currently in clinical development. The recommendations below are based on results from nonclinical studies, data from the Phase 1a study of BGB-3245, known risks associated with other RAF inhibitors, and data that are in the BGB-3245 IB.

8.2. Selected Adverse Events

8.2.1. Skin and Subcutaneous Tissue Disorders

A common and potential DLT of RAF inhibitors is skin and subcutaneous tissue disorders. While these are primarily Grades 1 and 2, appropriate early management of these AEs is necessary.

In a review of the emerging safety profile of BGB-3245, treatment emergent and drug-related AEs related to rash acneiform, rash maculopapular, and other dermatological toxicities were noted in approximately 70% of all participants who received at least 1 dose of BGB-3245 in the Phase 1a portion of the study (n=42). These events were noted to occur within the first 2 cycles of therapy with BGB-3245.

8.2.2. Rhabdomyolysis

As of September 2022, one case of Grade 3 rhabdomyolysis was reported from a participant who received BGB-3245 at 60 mg QD. The study drug was withheld, the event resolved, and the dose of BGB-3245 was reduced. Creatine phosphokinase laboratory tests should be performed to monitor the muscular effect of the study drug (see schedules in [Table 12](#) and [Table 14](#)). Participants should be informed about this potential risk and encouraged to promptly report relevant symptoms and signs, such as muscle pain, tenderness, and weakness with or without dark urine. Please see [Table 5](#) for dosing modification recommendations.

8.2.3. Nausea

In a review of the emerging safety profile of BGB-3245, treatment emergent and drug-related AEs related to nausea were noted in approximately 29% and 10%, respectively, of all participants who received at least 1 dose of BGB-3245 in the Phase 1a portion of the study (n=42). These events were noted to occur within the first 2 cycles of therapy with BGB-3245.

In the event of nausea, it is highly recommended that local standards of care therapies for antinausea therapy be instituted.

8.2.4. Pneumonitis

Pneumonitis is a rare form of interstitial lung disease that occurs commonly with immune checkpoint inhibitors (ICIs), various systemic chemotherapies, and targeted therapies, including RAF inhibitors. This usually presents with nonspecific symptoms such as a nonproductive cough

and dyspnea, and participants may require supplemental oxygen therapy. Thoracic imaging of pneumonitis typically reveals ground-glass opacities, reticular infiltrates, and traction bronchiectasis with subpleural sparing. Management of these events usually involves oral corticosteroids at 0.5 to 1 mg/kg/day with a slow taper.

In the review of the Phase 1a portion of this study, there were 9 participants with 10 events of dyspnea noted. Of these, 6 events were considered serious, while 4 were considered non-serious. All 9 of these participants had metastatic disease to their lungs. These events were unrelated to BGB-3245. There were 2 events of cough, both nonserious. Both participants had lung metastases, and these were not considered related to BGB-3245. Due to the history of prior use of ICIs and pneumonitis as a known risk associated with other RAF inhibitors, it is highly recommended to measure the participant's pulse oximetry at baseline, on Cycle 1 Day 1, Day 1 of each cycle, and as clinically needed. This information will be entered into the eCRF.

8.2.5. Acute Kidney Injury

Acute kidney injury has been reported with RAF inhibitors.

One participant was reported with drug-related Grade 3 Acute kidney injury started 14 days after first dose, with concurrent events of maculopapular rash, fever, and hypotension. The events resolved after drug discontinuation.

8.2.6. Drug-Induced Liver Injury (DILI) and Hy's Law

Abnormal values of AST and/or ALT levels concurrent with abnormal elevations in TBIL level that meet the criteria outlined below and not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis (eg, elevated ALP) are considered potential cases of drug-induced liver injury (eg, potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury, including Hy's law, depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST or ALT and TBIL baseline values within the normal range who subsequently present with AST or ALT values $\geq 3 \times \text{ULN}$ concurrent with a TBIL value $\geq 2 \times \text{ULN}$ with no evidence of hemolysis and an ALP value $\leq 2 \times \text{ULN}$ or other findings indicating an absence of cholestasis;
- For participants with baseline ALT or AST values above the ULN, AST or ALT value ≥ 2 times the baseline values should be used in the definition mentioned above.

The participant should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include ALB, creatine kinase, TBIL, direct and indirect BIL, gamma glutamyl transferase, PT/INR, and ALP.

A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

No case of DILI has been reported from the current study.

8.2.7. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Participants will be assessed for safety (including laboratory values) according to the schedules in [Table 12](#) and [Table 14](#).

Participants will be evaluated clinically and with standard laboratory tests within 21 days prior to administration of study drug and at regular intervals after administration of study drug. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc), and other assessments. In addition, participants will be monitored for the development of any signs or symptoms of infection.

For Cycle 1 Day 1, administration of study drug will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available. The remaining cycles may be completed as outpatients at the discretion of the treating investigator.

All AEs will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 (+ 7) days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first.

Investigators are instructed to report all events (including AEs and reports of pregnancy). In addition, the sponsor medical monitor or safety physician will review and evaluate observed AEs on a regular basis. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such AEs, are outlined in the following sections.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

Examples of what does not need to be captured as an AE:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

NOTE: The following are not considered SAEs for the seriousness criterion of hospitalization (but may be considered serious if any other criteria are met):

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered "important medical event" or event life threatening)
- An elective surgery or procedure, planned prior to signing consent for a condition that did not worsen during the course of the study
- Admissions as per protocol for a planned medical/surgical procedure or for standard diagnostic purposes including but not limited to surgical biopsy or resection
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

Special Situations

Special situations are to be reported within the AEs case report forms in the clinical database and via an SAE reporting form (the latter only if assessed as serious). Special situations include the following: Abuse, Misuse, Occupational Exposure (inadvertent/accidental), and Medication Error with the study product whether or not the participant was administered the wrong product, dose, etc (eg, study product name confusion). Definitions of special situations are as follows:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects
- Misuse: Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the protocol
- Occupational Exposure: An exposure to a medicinal product as a result of one's professional or nonprofessional occupation
- Medication Error: An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the participant

When any special situation, AE, adverse event of special interest (AESI) (see [Section 8.6.2](#) for AESI details), or SAE occurs, it is the responsibility of the investigator to review all documentation (ie, hospital progress notes, laboratory results and diagnostics reports) relative to the AE, AESI or SAE. The investigator will then record all relevant information regarding an AE, AESI, or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all participant identifiers on any copies of medical records will be redacted by the site prior to sending these documents to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess severity for each AE, AESI, and SAE reported during the study. AEs, AESIs, and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Adverse events that are not specified in the NCI-CTCAE v5.0 will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in [Section 8.4](#).

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE, AESI, or SAE, using best clinical judgment. Alternative causes, such as natural

history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE, AESI, or SAE to the study drug should be considered and investigated. The investigator should refer to IB of BGB-3245 in the determination of his/her assessment.

2-Point Causality Assessment

There may be situations when an AESI or SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes assessment of causality for every AESI or SAE prior to transmission of the AESI or SAE report/eCRF to the sponsor, because the causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information, amending the AESI or SAE report/eCRF accordingly.

The causality of each AE, AESI, or SAE should be assessed and classified by the investigator as “related” or “not related.” An AE, AESI, or SAE is considered related if there is “a reasonable possibility” that the AE, AESI, or SAE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the event to the administration of study treatment/study procedure;
- Whether an alternative etiology has been identified;
- Mechanism of action of the study drug; and
- Biological plausibility

An event should be considered “related” to study drug if any of the following are met:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out;
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely; or
- There is some evidence to suggest a causal relationship (ie, the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (ie, the participant’s clinical condition or other concomitant events).

8.3.4. Follow-Up to Adverse Events, Adverse Events of Special Interest, Serious Adverse Events, and Reports of Pregnancy

After the initial AE, AESI, or SAE report, the investigator is required to proactively follow each participant and provide further information to the sponsor on the participant’s condition.

All AEs, AESIs, and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs, AESIs, and SAEs will be followed until resolution; the condition stabilizes or is considered chronic; the AE, AESI, or SAE is otherwise explained; the participant is lost to follow-up; or the participant withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE, AESI, or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

Details of all pregnancies in female participants and female partners of male participants will be collected from first administration of study treatment until the outcome of the pregnancy is known (see [Section 8.6.6](#)).

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE, AESI, SAE, or report of pregnancy. The investigator is obligated to assist. If a participant dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in [Section 8.6.2](#).

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (ie, serum chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (ie, ECGs or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs, AESIs, or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and that worsen significantly during the study. The definition of clinically significant is based on the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and BIL $5 \times$ ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of

the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening;

NOTE: The term “life-threatening” in the definition of “serious” refers to an AE in which the participant was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization;

NOTE: In general, hospitalization signifies that the participant was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.

- Results in disability/incapacity;

NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (ie, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect; or
- Is considered a significant medical AE by the investigator based on medical judgment (ie, may jeopardize the participant or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

Refer to [Section 8.6.4](#) and [Section 8.6.5](#) regarding the reporting of PD and death.

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is judged as unexpected. An event is considered “unexpected” if it is not listed as expected in the reference safety information section of the IB at the time of occurrence.

8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the first administration of the study drug, only SAEs should be reported.

After first administration of the study drug(s), all AEs, AESIs, and SAEs, regardless of relationship to study drug(s), will be reported until either the post-study Safety Follow-up visit at 30 (+ 7) days after the last dose of study drug or until the initiation of subsequent anticancer therapy, whichever occurs first. A report of pregnancy in a female participant or the female partner of a male participant will be followed-up until the outcome of the pregnancy is known (see [Section 8.3.4](#) and [Section 8.6.6](#)). Investigators are not obligated to actively seek AE or SAE information after conclusion of the 30-day safety follow up period. However, if the investigator becomes aware of any AEs, AESIs, or SAEs, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

8.6.2. Adverse Events of Special Interest

Adverse events of special interest are defined as nonserious or serious AEs that are of scientific and/or medical concern specific to the sponsor's product, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. AESIs are designated by the investigator and should be reported to the sponsor in the same manner as SAEs. AESIs for BGB-3245 are provided in Table 9.

Table 9: Adverse Events of Special Interest for BGB-3245

Musculoskeletal (reported as AESI if Grade $\geq$ 2)
Rhabdomyolysis
Myalgia
Muscular weakness
Muscle spasms
Musculoskeletal (reported as AESI if Grade $\geq$ 3)
Creatine phosphokinase increased
Cardiac Disorders (reported as AESI if Grade $\geq$ 2)
Atrial fibrillation
Cardiac failure
Renal Disorders (reported as AESI if Grade $\geq$ 2)
Acute kidney injury
Skin Disorders (reported as AESI if Grade $\geq$ 3)
Drug-induced hypersensitivity
Angioedema
Rash
Rash acneiform

Table 9: Adverse Events of Special Interest for BGB-3245 continued

Rash maculopapular
Hepatic Disorders (reported as AESI if Grade $\geq$ 3)
Aspartate transaminase increase
Alanine transaminase increase
Hematological Disorders (reported as AESI if Grade $\geq$ 2)
Platelet Count Decreased/Thrombocytopenia
Constitutional (reported as AESI if Grade $\geq$ 2)
Pyrexia
Respiratory Disorders (reported as AESI if Grade $\geq$ 2)
Pneumonitis

Abbreviation: AESI, adverse event of special interest.

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an AESI or SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 10.

Table 10: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time Frame for Submitting Initial Report	Time Frame to Request Follow-Up Information	Time Frame for Submitting Follow-Up Report	Documentation Method for Initial or Follow-Up Report	Reporting Method
All SAEs and AESIs	Within 24 hours after first knowledge of the event	As expeditiously as possible	Within 24 hours after receipt of follow-up information	SAE report form or Pregnancy/Breast feeding Report Form provided for the study	Email or fax as provided on the respective form

Abbreviations: AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE and/or AESI has occurred in a participant, he/she is to report the information to the sponsor within 24 hours as outlined above in [Section 8.6.1](#). The SAE/AESI report will always be completed as thoroughly as possible, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE/AESI, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE/AESI and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE/AESI as described in [Section 8.3.3](#).

The sponsor will provide contact information for SAE/AESI receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in [Section 8.6.2.1](#). The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All SUSARs (as defined in [Section 8.6.2](#)) will be submitted to all applicable regulatory authorities and investigators for BGB-3245 studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

8.6.3. Eliciting Adverse Events

The investigator or designee will ask open-ended questions to identify AEs, which may include asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Progressive Disease

PD or disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE or SAE term using the wording such as *disease progression* or *progression of disease*. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the AE or SAE term(s).

For instance, a participant presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a participant experienced a fatal multiorgan failure due to disease progression, the term "multiorgan failure" should be reported as the SAE with death as the outcome instead of reporting "fatal disease progression" or "death due to disease progression."

8.6.5. Deaths

Death is an outcome and not usually considered an SAE. The cause of death should be reported as the SAE with the serious criteria reported as death and the outcome of the participant noted as death. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, “death,” “death of unknown cause,” or “death unexplained”).

8.6.6. Recording Pregnancies

If an investigator learns that a female participant or the female partner of a male participant becomes pregnant while the participant is receiving study drug(s) or within 180 days after the last dose of BGB-3245, a pregnancy report form must be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. A separate consent must be obtained for a female partner of a male participant. Details of all pregnancies in female participants and female partners of male participants will be collected from first administration of study treatment until the outcome of the pregnancy is known. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date; however, if any congenital anomaly is reported or there is any reported SAE for the child, additional follow-up might be requested. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Similarly, abnormal pregnancy outcome (eg, fetal death, stillbirth, ectopic pregnancy) or congenital anomaly/birth defect in a child born to a participant exposed to the study drug should be recorded and reported as an SAE.

8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the reference safety information section of the BGB-3245 IB.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS[®] Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable. No missing data will be imputed generally, and statistical methods will be primarily descriptive in nature. Details of the statistical analyses will be included in a separate SAP.

9.1. Statistical Analysis

9.1.1. Randomization Methods

Not applicable.

9.1.2. Analysis Populations

The analysis populations will include:

- The Safety Population will include all participants who received at least 1 dose of study drug.
- The Efficacy Evaluable Population will include all dosed participants who have radiologically confirmed evaluable disease at baseline, and at least 1 evaluable post-baseline radiological tumor response assessment.
- The DLT Evaluable Population included participants who received at least 80% of the assigned dose of BGB-3245 during the dose-escalation phase (Phase 1a) or who experienced a DLT during the dose-escalation phase (Phase 1a).
- The PK Population will include all dosed participants for whom valid BGB-3245 PK parameters can be estimated.
- The PDx Population will include all participants with valid BGB-3245 PDx sampling after treatment with BGB-3245.

9.1.3. Participant Disposition

The number of participants treated, discontinued from study drug, and/or the study and those with major protocol deviations will be counted. The primary reason for study drug and/or study discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrawn consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Major protocol deviations will be summarized and listed by category of deviation.

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time since

initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include number of prior systemic treatment, tumor node metastasis classification of malignant tumors staging, sex, ECOG performance status, country, race, and metastatic site.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification using the Medical Dictionary for Regulatory Activities (MedDRA) version (v) 21 or higher. Prior and concomitant medications will be summarized and listed by drug and drug class. Prior medications will be defined as medications that stopped before the first administration of study medication. Concomitant medications will be defined as medications that (1) started before the first administration of study medication and were continuing at the time of the first administration of study medication, or (2) started on or after the date of the first administration of study medication up to 30 days after the participant's last dose.

9.1.6. Efficacy Analysis

The efficacy endpoints will be analyzed using the Evaluable Population except for PFS and OS which will be analyzed using the Safety Population.

Tumor response was assessed by the investigator in Phase 1a. Tumor response will be assessed by the investigator and images will be collected for central review in Phase 1b. The investigator's assessment of the tumor response will be used for treatment decisions (continue vs. discontinue the treatment) in both phases of the study.

A participant will be considered *evaluable* for the Phase 1b dose expansion if they provide a baseline radiological tumor assessment at the Screening Visit and at least one evaluable post baseline radiological tumor response assessment.

For the analysis of ORR, DCR, and CBR, summary tables presenting the number and proportion of responders with the 2-sided exact (Clopper-Pearson) 95% confidence interval (CI) for response rates will be presented. Summary of each response category of the BOR will be presented as well. Waterfall plots of maximum tumor shrinkage per participant will be presented.

The time-to-event endpoints, including PFS, DOR, DSD, and OS will be analyzed by Kaplan-Meier methods. The survival functions of the time-to-event endpoints will be summarized for 25th percentile, median, and 75th percentile and their 95% CI. The rates of PFS, DOR, DSD, and OS at Month 3 and every subsequent 3 months as appropriate and their 95% CI will be derived based on Kaplan-Meier estimates. In addition, the graphs of Kaplan-Meier estimates of survival functions will be presented.

9.1.6.1. Rationale for the Expansion of BRAF Fusion Participants

As of 19 January 2024, 3 out of 4 evaluable RAF fusion participants were assessed as having responses in Group 2 of the ongoing Phase 1b study. To further assess the clinical efficacy and safety of brimarafenib in participants, the participant cohort with advanced solid tumors harboring a BRAF fusion will be further expanded (Group 2 BRAF Fusion Expansion) to allow a

total of 15 evaluable participants, including those evaluable from Group 2. This number of participants with BRAF fusion will provide an estimate on the response rate (ORR = CR+PR) with adequate assessment of the clinical activity of brimarafenib for these participants based on ORR.

As presented in Table 11 below, 15 participants allows for the determination of whether brimarafenib treatment would result in an ORR of greater than 20%, as the lower bound of the exact 95% CI excluding this threshold for various responder scenarios. As an example, if seven responders are observed in 15 evaluable participants, the lower bound of the 95% CI will be 21.3%, excluding a 20% threshold. If seven responders are observed with less than 15 evaluable participants, enrollment into this cohort could be stopped prior to getting a total of 15 evaluable participants with BRAF fusions.

The SMC will consider these statistical properties as a guide to recommend an adaptation of the total sample size of 15 evaluable participants with BRAF fusions. For a final assessment the totality of the data including DOR and PFS as well as safety data will be considered.

Table 11: Responder Rates and 95% CI for Different Sample Size and Responder Rate Scenarios for BRAF Fusion Participants

Total number of participants	Number of responders n (%)	Lower bound of 95% CI	Upper bound of 95% CI
15 ^a	6 (40.0%)	16.3%	67.7%
	7 (46.7%)	21.3%	73.4%
	8 (53.3%)	26.6%	78.7%
	9 (60.0%)	32.3%	83.7%

Abbreviations: BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B

^a Enrollment could be stopped for efficacy with less than 15 evaluable participants harboring BRAF fusions.

9.2. Safety Analyses

Safety endpoints (other than DLTs) will be summarized using the Safety Population. All summaries of safety will be by dose level for Phase 1a and by participant group (tumor type) for Phase 1b.

9.2.1. Extent of Exposure

Treatment exposure will be summarized descriptively. Measures of extent of exposure include the number of treatment cycles received, duration of exposure, and dose intensity for the study period. The number of participants with dose delay and reason for dose discontinuation will also be summarized, as appropriate.

9.2.2. Adverse Events

Adverse events will be coded using the current version of MedDRA, and AE data will be summarized by SOC and PT. Adverse events will also be summarized by worst AE severity/grade and AE relationship to study treatment. The number of SAEs and AEs which led to discontinuation of study treatment will also be summarized. All AE summaries will be restricted to TEAEs only.

For Phase 1a, DLTs were summarized for the DLT Evaluable Population.

A by-participant AE data listing, including verbatim term, MedDRA SOC and PT, severity, outcome, and relationship to study treatment, will be provided. Separate listings will be generated for serious AEs and AEs leading to discontinuation of study treatment.

9.2.3. Laboratory Analyses

All hematology, chemistry, and coagulation (continuous variables) parameters will be summarized using descriptive statistics for all protocol scheduled time points, including change from baseline for all post-dose assessments. Number of participants with abnormal laboratory test values including their clinical significance (if available) will be summarized as well. Shift tables from baseline to post-dose assessments will also be generated for each safety laboratory parameter with values of “within normal limits,” “high,” and “low” used for the shift categories. Laboratory values will be compared with the normal range of the laboratory, and values that fall outside of the normal ranges will be flagged as: H (High) and L (Low) in the data listings.

Dipstick urinalysis results evaluation will be summarized at each protocol scheduled time point. Microscopy data, if available, will be listed.

9.2.4. Vital Signs

Vital sign measurements and changes from baseline will be summarized at each protocol scheduled time point.

9.2.5. Physical Examination

Newly occurring or worsening clinically significant abnormalities identified on physical examination will be captured as AEs and will not be summarized or listed separately.

9.2.6. 12-Lead Electrocardiogram

Descriptive statistics will be calculated for 12-lead ECG parameters, including changes from baseline for all time points assessed. In addition, the overall interpretation of 12-lead ECG results will be classified using frequency counts and percentages for the categories of normal, abnormal not clinically significant, and abnormal clinically significant for all time points assessed, as applicable. In addition, the categorical analysis of QTc outliers (number [%] of maximum individual absolute QTc values and maximum individual QTc change from baseline) will be presented according to the ICH E14 guideline. Further details will be provided in the SAP.

9.2.7. Eastern Cooperative Oncology Group Performance Status

Shifts from baseline in ECOG performance status will be summarized descriptively using frequency counts and percentages at the protocol scheduled time points.

9.2.8. Ophthalmological Examination

The overall assessment by the ophthalmologist (normal, abnormal not clinically significant, abnormal clinically significant) will be summarized. In case the result of the ophthalmologist's examination is abnormal in only 1 eye, then the result will be summarized as abnormal for the

overall eye examination. The results of the eye examination will be listed by participant, and by eye, for each method (visual acuity, intraocular pressure, slit lamp, dilated fundoscopy, OCT).

9.3. Pharmacokinetic Analysis

Pharmacokinetic data will be analyzed using the PK Population. BGB-3245 PK variables (ie, AUC_{last} , $AUC_{0-\infty}$, C_{max} , T_{max} , $t_{1/2}$, apparent clearance, and V_z/F) will be calculated after single dosing in Phase 1a, if sufficient data are available. In addition, $AUC_{last,ss}$, AUC_{tau} , $C_{max,ss}$, and $T_{max,ss}$ will be calculated in Phase 1a, if sufficient data are available. The PK parameters, including those of any potential metabolite(s) of BGB-3245, will be calculated as appropriate using noncompartmental methods and summary statistics will be provided. In Phase 1b, PK parameters such as C_{trough} at steady state will be summarized, and additional PK parameters may be derived if supported by data. BGB-3245 (or possible major metabolites) plasma concentration data and PK parameters will be tabulated and summarized according to the protocol-specified time points. Descriptive statistics will include means, medians, minimums, maximums, standard deviation, coefficient of variation (CV), geometric mean, and geometric %CV as appropriate. Mean plasma concentrations will also be plotted against time for each dose level. Additional PK analyses may be conducted as appropriate.

Exposure-response (for efficacy or safety endpoints) analysis may be carried out if supported by data. Correlation between PK and Biomarker endpoints may be explored as appropriate. Results of such analyses may be reported separately from the clinical study report.

9.4. Other Exploratory Analyses

Biomarker data will be analyzed using the biomarker evaluable and PDx population. Summary statistics will be provided for PDx biomarkers, including but not limited to mutation, transcription, and phosphorylation profiles of MAPK pathway signaling in baseline biopsies, on-treatment biopsies, and longitudinal blood samples. An exploratory analysis on a potential correlation of these PDx markers with the dose, PK, safety, and antitumor activity will be performed as appropriate. The primary predictive biomarker analysis is based on a subset of the participants with aberrations in the MAPK pathway such as oncogenic BRAF, KRAS, NRAS, NF1 mutations, and RAF fusions. Exploratory analyses of other candidate predictive biomarkers will be conducted similarly. Depending on the data available, the analysis for biomarkers will be descriptive in nature. Details will be provided in the SAP, as applicable.

9.5. Sample Size Consideration

No formal statistical calculation of sample size will be used, and the sample size is empirical. The study plans to enroll.

- Phase 1a: Up to 60 participants for the dose escalation until MTD and/or RP2D determination
- Phase 1b: Approximately 105 participants will be treated to achieve up to 75 evaluable participants (40 evaluable participants in Group 1, 20 evaluable participants in Group 2, including up to 15 evaluable participants in Group 2 BRAF Fusion Expansion as per [Section 9.1.6.1](#)). Groups 1 and 2 will be evaluated separately.

Participants who fail to meet the criteria for being evaluable will be replaced. Each group may be closed due to futility or clinical efficacy based on statistical evaluation or insufficient participant recruitment. If promising preliminary efficacy results have been observed in any of the arms after treating all planned participants (ie, higher ORR or longer PFS), more participants could be added to that arm to further assess the efficacy before moving into Phase 2/3 clinical development. This additional enrollment in the expansion cohort may occur only after the amendment to the protocol supporting this action is approved by the IRB or the Ethics Committee.

- The rationale for the sample size for the expansion of the BRAF fusion participant cohort is presented in [Section 9.1.6.1](#).

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

An SMC was established and includes the sponsor's representatives, contract research organization's medical monitor, and at least 2 participating investigators. The SMC reviews all available safety, preliminary efficacy, PK, and exploratory data and makes recommendations on dose escalation, dose modification, and dose selection for Phase 1a and Phase 1b. The SMC may also be called upon by the sponsor on an ad hoc basis where applicable to the conduct of the study.

A separate charter will further detail the role of the SMC (available on request).

10.2. Communication

The sponsor plans to have regular communications with all study sites (study investigators and coordinators) regarding:

- study enrollment status
- any significant safety findings
- decisions on dose escalation
- considerations for protocol amendments

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive participant data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor or representatives of the sponsor may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor (or representatives of the sponsor) access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, participants' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), participant drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from the sponsor and quantities dispensed to participants, including lot number, date dispensed, participant identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with the sponsor's requirements. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator (or designated personnel) and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/IEC.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to participants already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Where the investigator is responsible for submission to

the IRB/IEC, the final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to participate. Where the principal investigator is responsible for submission to the IRB/IEC, the final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Participants must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the participant or the participant's legally authorized representative. All signed and dated ICFs must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Participant and Data Confidentiality

The investigator, institution, sponsor, and site will maintain confidentiality and privacy standards for the collection, storage, transmission, and processing of participants' personal and medical information by following applicable laws and regulations related to the confidentiality, use, and protection of such information, including the ICH Good Clinical Practice Guideline, as implemented locally. Such laws may be more stringent than the requirements in this protocol.

The investigator and site shall code the personal and medical information obtained during the study with a unique participant identification number assigned to each participant enrolled in the study. The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Unless required to be provided by laws or regulations or specifically requested in exceptional circumstances by the sponsor or its representatives, the investigator and site must ensure that any personal and medical information transmitted to sponsor or its service providers is: 1) required by the protocol, and 2) appropriately de-identified (eg, via redaction and/or coding with the participant identification number) to ensure the following information about participants are NOT shared:

- names or initials (full or partial);
- full dates of birth;
- contact information (such as phone numbers, home or email addresses);

- numerical identifiers (eg, hospital or medical record, government, health insurance or financial account numbers) other than participant identification numbers assigned as part of this study;
- geographic identifiers smaller than a state, province or local equivalent (such as city, county, zip code or other equivalent geographic identifiers); or
- information about marital status, family or household members, employment, sex life, sexual preference, or other sensitive data that is not relevant to the study.

Participant personal and medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the participant), unless permitted or required by law.

In limited circumstances, such as in connection with insurance purposes or participant support services ancillary to certain study sites (eg, for participant travel or reimbursement), the investigator and site may provide certain of this personal information to the sponsor or its representatives. Such personal information may not be provided as part of the study protocol (eg, as part of the eCRF, on samples or reports submitted to the central lab, on safety reporting forms (except in China) or on product dispensing logs provided to the sponsor, etc).

Investigator and site must use only the specific forms and clinical trial systems, eg, the electronic data capture (EDC) system and any secure file transfer platforms designated by sponsor for sharing and transfers of personal and medical information.

In the event of a breach of the confidentiality of a participant's personal and medical information, the investigator, site, and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable laws. If the sponsor identifies personal or medical information that was not properly de-identified, it may be required to report the disclosure under local applicable laws. Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare for treatment purposes where allowed by local law or the participant's signed ICF.

Information generated during this study must be available for inspection upon request by representatives of the US FDA, the China National Medical Products Administration (China NMPA), and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator agrees that all information received from the sponsor, including but not limited to the BGB-3245 IB, the BGB-3245-AU-001 protocol, eCRFs, the investigational drug (BGB-3245), and any other study information, are confidential and remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study includes confidentiality or privacy provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

For all clinical investigators, the sponsor is required to disclose the presence or absence of certain financial interests, as required, to the appropriate health authorities. Investigators are required to provide the sponsor with complete and accurate financial information in accordance with regulations to allow the sponsor to make these submissions. This is intended to ensure financial interests and arrangements of clinical investigators with the sponsor that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators (including any sub-investigators and co-investigators) are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last participant, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an EDC system. All study-related data collected or received by the investigator or study team shall be entered into the eCRF in a timely way, and no later than the contractual agreement. Exceptional circumstances should be agreed to, in writing, with the sponsor.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

14.1.2. Data Management/Coding

All final participant data, both eCRF and external data (eg, laboratory data), collected according to the protocol will be stored by the sponsor at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual participant's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration to data protection and medical confidentiality.

AEs and concomitant diseases/medical history will be coded using MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary.

14.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and/or 2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICFs, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Participant clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: participant hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening, and enrollment logs, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to at least 25 years in the European Union and Canada and at least 15 years elsewhere.

The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archival at an off-site facility or transfer of ownership or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the site.

Biological samples processed by the sponsor's designated laboratories may be retained at the conclusion of this study for the shorter of a period of up to 10 years or as allowed by your IRB/IEC.

14.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with this protocol, including carrying out the procedures and evaluations described in this protocol that occur at the sites overseen by the investigator. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the sponsor.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact participant safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.4. Publications and Data Sharing Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of the sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria ([International Committee of Medical Journal Editors 2016](#)).

After conclusion of the study, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media the results of the study only after the following conditions have been met:

- results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- if there is no such a publication within 2 years of study completion.

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. For details of the submission and review processes see your clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

14.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide all study data to the sponsor;

- Resolution and closure of all data queries;
- Accountability, reconciliation, and arrangements for unused study drug(s);
- Review of study records for completeness;
- Collection of all study documents for the trial master file filing according to GCP and local regulation; and
- Shipment of samples (including but not limited to those for PK, antidrug antibody, and biomarkers) to the designated laboratory for analysis according to protocol and laboratory manual requirements

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason.

Potential reasons for suspension or discontinuation include but are not limited to the following: safety or ethical issues or noncompliance with this protocol, GCP, the sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

14.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center or investigator, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a participant's medical records) are the sole property of the sponsor and will be kept confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a participant
- Study results that may be published as described in [Section 14.4](#)

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

15. REFERENCES

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16. APPENDICES

16.1. Schedules of Assessments

Table 12: Study Assessments and Procedures Schedule for Phase 1a

Phase 1a	Screening ^a	Treatment period										End-of-Treatment ^b	Safety Follow-up ^c
		Cycle 1 (30 Days, DLT period)							Cycle 2 (28 Days)		Cycle 3 and Subsequent Cycles (28 Days)		
Days (window)	-28 to -1	1	2	3	4	8 (± 1)	15 (± 2)	22 (± 2)	1 (+ 2)	15 (± 2)	1 (± 2)	≤ 7 days ²	30 (+ 7) days after last dose
Informed consent ^d	X												
Inclusion/exclusion criteria ^e	X												
Demographics/medical history/prior medications ^f	X												
Vital signs ^g	X	Refer to Table 13							Refer to Table13	X	Refer to Table13 for C3 and C4; X (≥ C5)	X	X
Height ^h	X												
Weight ⁱ	X	X							X		X	X	X
Physical examination ^j	X	X					X		X	X	X	X	X
ECOG performance status ^k	X	X							X		X	X	X
12-lead ECG ^l	X	Refer to Table13							Refer to Table13		Refer to Table13 for C3 and C4; X (≥ C5)	X	X
Hematology, serum chemistry ^m	X	X			X ^m	X	X		X	X	X	X	X

Table 12: Study Assessments and Procedures Schedule for Phase 1a continued

Phase 1a	Screening ^a	Treatment period										End-of-Treatment ^b	Safety Follow-up ^c
		Cycle 1 (30 Days, DLT period)							Cycle 2 (28 Days)		Cycle 3 and Subsequent Cycles (28 Days)		
Days (window)	-28 to -1	1	2	3	4	8 (± 1)	15 (± 2)	22 (± 2)	1 (+ 2)	15 (± 2)	1 (± 2)	≤ 7 days ²	30 (+ 7) days after last dose
Thyroid function test ⁿ	X										Starting at Day 1 of C4 and every 3 cycles thereafter		X
Coagulation ^o	X					As clinically indicated						X	X
Urinalysis ^p	X					As clinically indicated						X	X
Pregnancy test ^q	X								X		X	X	X
HBV and HCV ^r	X												
Review CD4 count for participants with known HIV	X												
LVEF assessment by ECHO or MUGA	X	As clinically indicated											
Adverse events ^s	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ^t	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood tumor biomarkers ^u	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)										X	
Tumor imaging ^v	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)										X	
Tumor tissues (archival or fresh) ^w	X	Optional Follow-up biopsy after disease progression											
PK blood sampling ^x		Refer to Table 13 (up to and including C4)											

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Table 12: Study Assessments and Procedures Schedule for Phase 1a continued

Phase 1a	Screening ^a	Treatment period										End-of-Treatment ^b	Safety Follow-up ^c
		Cycle 1 (30 Days, DLT period)						Cycle 2 (28 Days)		Cycle 3 and Subsequent Cycles (28 Days)			
Days (window)	-28 to -1	1	2	3	4	8 (± 1)	15 (± 2)	22 (± 2)	1 (+ 2)	15 (± 2)	1 (± 2)	≤ 7 days2	30 (+ 7) days after last dose
Study drug administration ^y		X			X	X	X	X	X	X	X		
Ophthalmology examination ^z	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)										X	

Abbreviations: AE, adverse event; CNS, central nervous system; CPK, creatine phosphokinase; CT, computed tomography; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PD, progressive disease; PK, pharmacokinetic.

^a Screening evaluations will be performed within 28 days between the signing of the informed consent form until the first administration of study medication. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the first administration of study drug may be used for screening assessments rather than repeating such tests. Screening evaluations may be repeated as needed within the Screening Period; however, screening tumor assessments should not be repeated unless clinically indicated. The investigator is to assess participant eligibility according to the latest screening assessment results. See [Section 7.1](#) for details regarding participant rescreening.

^b The End-of-Treatment visit is conducted within 7 days after the investigator determines that study drug will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End-of-Treatment visit, tests do not need to be repeated. Tumor assessment does not have to be repeated if it was performed within 8 weeks of the EOT visit or at a prior response evaluation that documented PD. ECG is not required at the End-of-Treatment visit provided that fewer than 14 days have passed since the last assessment.

^c The Safety Follow-up visit should be conducted 30 (+ 7) days after the last dose of study drug or before the initiation of a new anticancer treatment, whichever comes first. Participants who discontinue study drug due to a Grade ≥ 3 drug-related AE will be followed until the resolution of the AE (to Grade 1, baseline, or stabilization) or initiation of a new treatment, whichever comes first. If new anticancer therapy is inadvertently initiated before this Safety Follow-up (eg, without the knowledge of the study center team), a Safety Follow-up should be scheduled as soon as possible.

^d Written consent must be obtained prior to performing any protocol-specific procedure.

^e Inclusion and exclusion criteria. See [Section 4](#) for details.

^f Demographics/medical history/prior medications will be collected at Screening. See [Section 7.1.1](#) for details.

^g Vital signs will be collected at Screening and throughout the study. Vital signs include measurements of temperature, heart rate, pulse oximetry, and blood pressure (systolic and diastolic) after the participant has been sitting for at least 5 minutes. Refer to [Table 13](#) for the following timepoints that coincide with PK sample collection: Cycle 1 Day 1, 2, 3, 4, 8, and 15, and Day 1 of Cycle 2, 3, and 4. For all other timepoints including Day 1 of Cycle 5 and each Cycle thereafter, vital signs should be taken within 60 minutes pre-dose and within 60 minutes post-dose (except for screening).

^h Height is only required at Screening visit.

ⁱ Weight is to be recorded throughout the study using the same scales (where possible).

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- ^j Physical examination. During the Screening visit, a complete physical examination will be conducted, which includes an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological (ie, investigator should assess for rash acneiform, rash maculopapular, and other skin toxicities), 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.
- ^k ECOG performance will be assessed at the Screening visit, on Day 1 of each treatment cycle, the EOT visit, and the Safety Follow-up visit. See [Appendix 16.2](#) for details.
- ^l 12-lead triplicate ECG assessments are to be performed with the participant in semi-recumbent or supine position and rested silently for at least 5 minutes. Refer to [Table 13](#) for the following timepoints that coincide with PK sample collection: Cycle 1 Day 1, 2, 3, 4, 8 and 15, and Day 1 of Cycle 2, 3, and 4. For all other timepoints including Day 1 of Cycle 5 and each Cycle thereafter, ECG must be performed within 60 minutes pre-dose (except for screening) or as clinically indicated.
- ^m Hematology and serum chemistry. Local laboratory assessments on serum chemistry and hematology will be conducted, of which certain elements will be collected as specified in [Appendix 16.3](#). If these tests at Screening are not performed within 96 hours prior to the administration of study drug on Cycle 1 Day 1, these tests should be reviewed within 48 hours before study drug administration. For subsequent cycles, complete blood count with differential and serum chemistry should be performed and results reviewed within 48 hours before study drug administration. Note: Blood samples for CPK monitoring will be taken at screening; Cycle 1 Day 1, Day 4 (CPK only), Day 8, and Day 15; on Day 1 of every cycle from Cycle 2 onward; and at the EOT visit.
- ⁿ Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, and free T4) will be performed at Screening and Day 1 of every 3 cycles thereafter starting with Cycle 4 (eg, Cycles 4, 7, 10, etc), and at the Safety Follow-up visit.
- ^o Coagulation. Local laboratory assessments on coagulation will be conducted, of which certain elements will be collected as specified in [Appendix Section 16.3](#).
- ^p Urinalysis. Local laboratory assessments on urinalysis will be conducted, of which certain elements will be collected as specified in [Appendix 16.3](#).
- ^q Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first administration of study drug. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug on Day 1 of each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- ^r HBV and HCV tests will be performed at Screening and include HBV and HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). In addition, viral load assessment (HBV DNA or HCV RNA) will be done for participants with HBsAg positive or HCV antibody positive at Screening, respectively.
- ^s Adverse events will be collected from the time of the main study informed consent form is signed through 30 (+ 7) days after administration of last dose of study drug or initiation of new anticancer therapy, whichever occurs first.
- ^t Concomitant medications. See [Section 6](#) for permitted, prohibited, or restricted medications and therapies.
- ^u Peripheral blood tumor biomarkers. Whole blood will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 8 (- 1) weeks in the first 12 months and approximately every 12 (- 1) weeks thereafter through the EOT visit.
- ^v Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to first dose of study drug, and while on study approximately every 8 (- 1) weeks in the first 12 months and approximately every 12 (- 1) weeks thereafter. The same imaging technique should be used in a participant throughout the study. In addition, participants must have a CT/MRI scan of the brain at Screening to confirm no CNS metastasis.
- ^w Tumor tissue (archival or fresh) will be collected for purpose of biomarker analysis. Baseline tumor tissue sample is mandatory, either from archived tumor tissue or fresh tumor biopsies. A follow-up biopsy may be taken (ideally from the same tumor lesion which is readily accessible) after participant has disease progression (at EOT). Additional written participant consent is required for archived tumor tissue or fresh tumor biopsies. See [Section 7.5](#) for details.
- ^x Pharmacokinetic blood samples will be collected as per [Table 13](#).
- ^y Cycle 1 length will be 30 days, with a 2-day treatment-free period on Days 2 and 3. Participants will be treated by regular daily, oral dosing, from Day 4 of Cycle 1 and continue until the last dose of BGB-3245, by repeated treatment cycles of 28 days. See [Section 5](#) for study drug dosing instruction. Participants will be required to fast for 2 hours before and 2 hours after the administration of study drug on all days throughout the study, except on the days with PK assessments, when participants will be required to fast for 8 hours before and 2 hours after the administration of study drug.
- ^z Ophthalmology examination. Full ophthalmic assessment, including the visual acuity, intraocular pressure, slit lamp examination, and retinal assessment, should be performed at Screening, every 8 ($\pm$ 1) weeks during the first year and every 12 ($\pm$ 1) weeks thereafter as well as at the EOT visit. If participants report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at time, a prompt ophthalmological assessment is required with follow-up as needed.

Table 13: Phase 1a Pharmacokinetic Sampling

Procedure	Cycle 1											Cycle 2							Cycle 3	Cycle 4	Cycle 5, Day 1 and Subsequent Cycles	
	Day 1							Day 2	Day 3	Day 4	Day 8	Day 15	Day 1							Day 1		Day 1
Hours	Pre-dose ^a	1	2	3	4	6	8	24	48	72	Pre-dose ^a	Pre-dose ^a	Pre-dose ^a	1	2	3	4	6	8	Pre-dose ^a	Pre-dose ^a	Pre-dose ^a
ECG time points for PK sampling ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^c	X	X	X	X	X	X	X	X	X	X	Pre-dose and post-dose	Pre-dose and post-dose	X	X	X	X	X	X	X	Pre-dose and post-dose	Pre-dose and post-dose	Pre-dose and post-dose
PK sampling ^c	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	

Abbreviations: ECG=electrocardiogram; PK=pharmacokinetic.

Note: Actual drug dosing and PK sampling times must be documented by the sites and will be captured in the database.

General note: It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated time point.

Thus, the sequence at a particular time point is: 1) ECG; 2) vital sign assessments; 3) PK blood sample (to be performed at the precise protocol scheduled time); and 4) any other scheduled or unscheduled measurements at that time point.

Should a participant undergo an inpatient dose escalation or dose reduction (refer to [Section 3.1.1](#)), additional blood PK samples will be taken to determine the plasma concentration of BGB-3245. The samples should be taken on Day 1 of the second cycle of the new dose (ie, Cycle 2 Day 1 of escalated or reduced dose) and on Day 1 of the third cycle of the new dose (ie, Cycle 3 Day 1 of escalated or reduced dose). These samples should be taken pre-dose on the required day.

^a Within 60 minutes prior to dose.

^b The following window period exists for ECG and Vital signs, pre-dose timepoints are required within 60 minutes prior to dose, ±10 minutes for 1-hour post-dose, ±30 minutes for 2-5 hours post-dose, ±60 minutes for 8-72 hours post-dose.

^c The following window period exists for PK sampling; pre-dose timepoints are required within 60 minutes prior to dose, ±10 minutes for 1-2 hours post-dose, ±30 minutes for 3-8 hours post-dose, ±60 minutes for 24-72 hours post-dose.

Table 14: Study Assessments and Procedures Schedule for Phase 1b

Phase 1b	Screening ^a	Treatment period							End-of-Treatment ^b	Safety Follow-up ^c	Survival follow-up ^d
		Cycle 1 (28 Days)				Cycle 2		Cycle 3 and Additional Cycles			
Days (window)	-28 to -1	1	8 (± 1)	15 (± 2)	22 (± 2)	1 (± 2)	15 (± 2)	1 (± 2)	≤ 7 days	30 (+ 7) days after last dose	Every 3 months
Informed consent ^e	X										
Inclusion/exclusion criteria ^f	X										
Demographics/medical history/prior medications ^g	X										
Vital signs ^h	X	X	X	X	X	X	X	X	X	X	
Height ⁱ	X										
Weight ^j	X	X				X		X	X	X	
Physical examination ^k	X	X		X		X	X	X	X	X	
ECOG performance status ^l	X	X				X		X	X	X	
12-lead ECG ^m	X	X				X		X	X	X	
IRT contact	X	X	X	X	X	X	X	X	X		
Hematology, serum chemistry ⁿ	X	X	X	X	X	X	X	X	X	X	
Thyroid function testing ^o	X					Every 3 cycles after baseline, starting at C4				X	
Coagulation ^p	X	As clinically indicated							X	X	
Urinalysis ^q	X	As clinically indicated							X	X	
Pregnancy test ^r	X					X		X	X	X	
HBV and HCV ^s	X										
LVEF assessment by ECHO or MUGA	X	As clinically indicated									
Adverse events ^t	X	X	X	X	X	X	X	X	X	X	

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Table 14: Study Assessments and Procedures Schedule for Phase 1b continued

Phase 1b	Screening ^a	Treatment period							End-of-Treatment ^b	Safety Follow-up ^c	Survival follow-up ^d
		Cycle 1 (28 Days)				Cycle 2		Cycle 3 and Additional Cycles			
Days (window)	-28 to -1	1	8 (± 1)	15 (± 2)	22 (± 2)	1 (± 2)	15 (± 2)	1 (± 2)	≤ 7 days	30 (+ 7) days after last dose	Every 3 months
Concomitant medications ^u	X	X	X	X	X	X	X	X	X	X	
Peripheral blood tumor biomarkers ^v	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)							X		
Tumor imaging ^w	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)							X		
Tumor tissue (archival or fresh) for Groups 1 and 2 ^x	X					Optional after treatment discontinuation					
PK blood sampling ^y		Refer to Table 15 for PK sampling.									
Study drug administration ^z		X	X	X	X	X	X	X			
Survival status											X
Ophthalmology examination ^{aa}	X	Every 8 (minus 1) weeks (first year); Every 12 (minus 1) weeks (second year)							X		

Abbreviations: CNS, central nervous system; CPK, creatine phosphokinase; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IRT, interactive response technology; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PD, progressive disease; PK, pharmacokinetic; TSH, thyroid-stimulating hormone.

^a Screening evaluations will be performed within 28 days between the signing of the informed consent form until the first administration of study drug. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to the administration of study medication may be used for screening assessments rather than repeating such tests. Screening evaluations may be repeated as needed within the Screening Period; however, screening tumor assessments should not be repeated unless clinically indicated. The investigator is to assess participant eligibility according to the latest screening assessment results. See [Section 7.1](#) for details regarding participant rescreening.

^b The End-of-Treatment visit is conducted within 7 days after the investigator determines that study drug will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End-of-Treatment visit, tests do not need to be repeated. Tumor assessment does not have to be repeated if it was performed within 8 weeks of the EOT visit or at a prior response evaluation that documented PD.

^c The Safety Follow-up visit should be conducted 30 (+ 7) days after the last dose of study drug or before the initiation of a new treatment, whichever comes first. Participants who are discontinued from the study because of an unacceptable drug-related adverse event will be followed until the resolution of the adverse event to Grade 0-1, or stabilization, or until beginning of a new therapy for their cancer, whichever occurs first.

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- ^d Survival Follow-up information will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months (± 1 week) after the EOT/Safety Follow-up visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All participants will be followed for disease progression, death (survival), and subsequent anticancer therapy information unless a participant requests to be withdrawn from follow-up.
- ^e Written consent must be obtained prior to performing any protocol-specific procedure.
- ^f Inclusion and exclusion criteria. See [Section 4](#) for details.
- ^g Demographics/medical history/prior medications. See [Sections 9.1.4](#) and [9.1.5](#) for details.
- ^h Vital signs will include measurements of temperature, heart rate, pulse oximetry, respiratory rate, and blood pressure (systolic and diastolic) after the participant has been sitting for at least 5 minutes. Vital signs should be taken within 60 minutes pre-dose and within 60 minutes post-dose at each specified visit.
- ⁱ Height is only required at Screening visit.
- ^j Weight is to be recorded using the same scales (where possible) at each time point.
- ^k Physical examination. During the Screening visit, a complete physical examination will be conducted, which includes an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.
- ^l Eastern Cooperative Oncology Group. See [Appendix 16.1](#) for details.
- ^m Triplicate ECG assessments are to be performed with the participant in semi-recumbent supine position and rested for at least 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening within 14 days of Cycle 1 Day 1 as baseline, within 30 minutes pre-dose and at 1 hour (± 10 minutes) and 3 hours (± 10 minutes) after dosing on Cycle 1 Day 1 and Cycle 2 Day 1, within 30 minutes pre-dose dose at Day 1 of Cycle 3 and all subsequent cycles, as well as at End-of-Treatment visit and at the mandatory Safety Follow-up visit. Multiple time point ECGs beyond Cycle 2 Day 1 will not be required but may be obtained if clinically indicated.
- ⁿ Hematology and serum chemistry. Local laboratory assessments on serum chemistry and hematology will be conducted, of which certain elements will be collected as specified in [Appendix 16.3](#). If these tests at Screening are not performed within 96 hours prior to the administration of study drug on Cycle 1 Day 1, these tests should be repeated and reviewed within 48 hours before study drug administration. To accommodate sites whose lab facilities are off site, we will allow up to 72 hours for local lab collection and review prior to study drug administration, for all cycles. Note: Blood samples for CPK monitoring will be taken at screening; Cycle 1 Day 1, Day 8, and Day 15; on Day 1 of every cycle from Cycle 2 onward; and at the EOT visit.
- ^o Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, and free T4) will be performed at Screening and every 3 cycles thereafter (eg, Cycles 4, 7, 10, etc), and at the Safety Follow-up visit.
- ^p Coagulation. Local laboratory assessments on coagulation will be conducted, of which certain elements will be collected as specified in [Appendix 16.3](#).
- ^q Urinalysis. Local laboratory assessments on urinalysis will be conducted, of which certain elements will be collected as specified in [Appendix 16.3](#).
- ^r Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first administration of study drug. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- ^s HBV and HCV tests will include HBV and HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). In addition, viral load assessment (HBV DNA or HCV RNA) will be done for participants with HBsAg positive or HCV antibody positive at Screening, respectively.
- ^t Adverse Events will be collected from the time of the main study informed consent form is signed through 30 (+ 7) days after administration of last dose of study drug or initiation of new anticancer therapy, whichever occurs first.
- ^u Concomitant medications. See [Section 6](#) for permitted, prohibited, or restricted medications and therapies.
- ^v Peripheral Blood tumor biomarkers. Whole blood will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 8 (- 1) weeks in the first 12 months and approximately every 12 (- 1) weeks thereafter through the EOT visit.
- ^w Tumor imaging (either CT or MRI, with preference for CT) will be performed within 21 days prior to first administration of study drug, and while on study approximately every 8 (- 1) weeks in the first 12 months and approximately every 12 (- 1) weeks thereafter. The same imaging technique should be used in a participant throughout the study. In addition, participants must have a CT/MRI scan of the brain at Screening to confirm no CNS metastasis. If asymptomatic and stable brain metastases are noted, follow these according to the tumor imaging schedule. Sites will submit all CT and/or MRI scans to the central imaging core laboratory for Central Imaging Review. All images should be submitted within 2 business days of scan date. Refer to the Multi-Modality Participant Scanning Guide study reference manual for detail.

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- ^x Eligible participants must provide a tumor tissue sample as the baseline. Tumor tissue sample may come from the archival sample or from the fresh tumor biopsy. For Groups 1 and 2, fresh biopsies are optional after treatment discontinuation and require additional written consent.
- ^y Pharmacokinetic blood samples will be collected as per [Table 15](#) below.
- ^z See [Section 5](#) for study drug dosing instruction. Participants will be required to fast for 2 hours before and 2 hours after the administration of study drug on all days throughout the study, except on the days with PK assessments, when participants will be required to fast for 8 hours before and 2 hours after the administration of study drug.
- ^{aa} Ophthalmology examination. Full ophthalmic assessment, including the visual acuity, intraocular pressure, slit lamp examination, and retinal assessments, should be performed at Screening, every 8 ($\pm$ 1) weeks during the first year and every 12 ($\pm$ 1) weeks thereafter as well as at the EOT visit. If participants report new visual disturbances such as diminished central vision, blurry vision, or loss of vision at time, a prompt ophthalmological assessment is required with follow-up as needed.

Table 15: Phase 1b Pharmacokinetic and Pharmacodynamic Sampling

Treatment Cycle	Day	Timepoint (hours post-dose) ^a	PK Sampling
Cycle 1 (28 Days)	1	0 (Pre-dose)	X
		1	X
		3	X
	8	0 (Pre-dose)	X
	22 (± 2)	0 (Pre-dose)	X
		2 to 4	X
Cycle 2 (28 Days)	1	0 (Pre-dose)	X
		1	X
		3	X
Cycle 3 (28 Days)	1	0 (Pre-dose)	X
Cycle 4 (28 Days)	1	0 (Pre-dose)	X
Cycle 6 (28 Days)	1	0 (Pre-dose)	X
Cycle 8 (28 Days)	1	0 (Pre-dose)	X
Cycle 10 (28 Days)	1	0 (Pre-dose)	X
Cycle 12 (28 Days)	1	0 (Pre-dose)	X
Every 3rd Cycle [Year 2]	1	0 (Pre-dose)	X
Treatment Discontinuation		2 to 4	X

Abbreviations: ECG, electrocardiogram; eCRF, electronic case report form; PK, pharmacokinetic; T_{max}, time to maximum observed plasma concentration.

Note: Actual drug dosing and PK sampling times must be documented by the sites and will be captured in the database.

General note: It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) ECG; 2) vital sign assessments; 3); PK blood samples (at the protocol scheduled time) and 4) any other scheduled or unscheduled measurements at that time point.

Should a participant undergo an inpatient dose reduction, additional blood PK samples will be taken to determine the plasma concentration of BGB-3245. The samples should be taken on Day 1 of the second cycle of the new dose (ie, Cycle 2 Day 1 of reduced dose) and on Day 1 of the third cycle of the new dose (ie, Cycle 3 Day 1 of reduced dose). These samples should be taken pre-dose on the required day.

^a Sampling window: Within 1 hour prior to dosing, ± 10 minutes for timepoints hour 1 to hour 3. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the sampling window will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and eCRF. These timepoints stipulated are dependent on the observed T_{max} and will be confirmed from Phase 1a data.

16.2. 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, ie, light housework, 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

[Oken 1982](#)

16.3. Clinical Laboratory Assessments

Clinical Chemistry	Hematology	Coagulation	Urinalysis	Hormones
Alkaline phosphatase	RBC count	PT	Appearance	TSH
Alanine aminotransferase	Hematocrit	aPTT	Color	Free T3
Aspartate aminotransferase	Hemoglobin	International	pH	Free T4
Albumin	Platelet count	Normalized	Specific gravity	Testosterone ^c
Amylase	WBC count with 5-part differential ^a	Ratio	Glucose	
Total bilirubin			Protein	
Blood urea nitrogen or equivalent (uric acid or urate)			Ketones	
Potassium			Bilirubin	
Sodium			Urobilinogen	
Calcium			Blood	
Chloride				
CPK/CK ^b				
Creatinine ^c				
eGFR (by CKD-EPI calculation) ^c				
Glucose				
Lactate dehydrogenase				
Phosphate				
Total protein				
HBsAg, antibodies against HBsAg, HBcAb, and HCV serology				

Abbreviations: aPTT, activated partial thromboplastin time; B-HCG, beta-human chorionic gonadotropin; CK, creatine kinase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPK, creatine phosphokinase; HBsAg, Hepatitis B surface antigen; HBcAb, hepatitis core antibody; HCV, hepatitis C serology; mCRCP, metastatic Castration-resistant Prostate Cancer; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; PT, prothrombin time; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell.

^a Both the absolute number and the proportion (%) of each cell type will be reported for the 5-part differential WBC. This includes neutrophils, basophils, eosinophils, lymphocytes, and monocytes.

^b For Grade 3 or higher CK/CPK elevations, it is recommended to monitor and measure isozymes (CPK1, 2, and 3). Evaluation for presence of myoglobin with blood test or with urinalysis is also recommended (See [Section 5.4.2](#)).

^c Testosterone test is only applied for participants with mCRCP. However, the testosterone levels do not need to be checked if the participant has undergone surgical castration for > 4 months. Participants receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM).

^d Creatinine will be used for calculation of creatinine clearance and estimated glomerular filtration rate using the equation provided in [Appendix 16.8](#).

^e At screening only to establish eligibility and/or baseline renal function. See [Section 16.8](#) for the CKD-EPI formula.

16.4. Contraception Guidelines and Definitions of “Women of Childbearing Potential,” “No Childbearing Potential”

Contraception Guidelines

The Clinical Trials Facilitation Group’s recommendations related to contraception and pregnancy testing in clinical trials includes the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)

NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the participant’s usual and preferred lifestyle.

Periodic abstinence (ie, calendar, ovulation, symptothermal, and post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of “Women of Childbearing Potential,” “Women of No Childbearing Potential”

As defined in this protocol, “women of childbearing potential” are female participants who are physiologically capable of becoming pregnant.

Conversely, “women of no childbearing potential” are defined as female participants meeting 1 of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
 - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
 - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

16.5. New York Heart Association Functional Classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, (eg, walking short distances [20-100 meters]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

16.6. The Response Evaluation Criteria in Solid Tumors Guidelines, Version 1.1

The text below was obtained from the following references:

[Eisenhauer 2009](#) and [Schwartz 2016](#).

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (version 1.1). Changes in only the largest diameter (unidimensional 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. The use of calipers for tumor lesion measurement will not be permitted in this study.

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) and;
- 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.

B1 Lesions:

- B1 scan, PET scan, or plain films are not considered adequate imaging techniques to measure b1 lesions. However, these techniques can be used to confirm the presence or disappearance of b1 lesions;
- Lytic b1 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; and
- Blastic b1 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) because they are, by definition, simple cysts; and
- 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 participant, these are preferred for selection as target lesions.

Lesions With Prior Local Treatment:

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

Target Lesions:

All radiologically 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 because 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 $\times$ 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 nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological 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.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget 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 nontarget lesions involving the same organ as a single item on the case record form (ie, “multiple enlarged pelvic lymph node” or “multiple liver metastases”).

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation. 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 being followed cannot be imaged but are accessible by clinical examination. Note that calipers will not be permitted for the measurements of tumor lesions in this study.

When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken because it is more objective and may also be reviewed at the end of the study.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- 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. 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 (ie, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be

taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- 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 studies where recurrence following CR or surgical resection is an endpoint.
- Tumor markers: Tumor markers cannot independently be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.
- 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 (ie, 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 to differentiate between response (or stable disease) and PD.

Response Criteria:

Evaluation of Target Lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) 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 1 or more new lesions is also considered progression).
- Stable Disease: 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 CR criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, 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 (ie, 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 on the eCRF. If it is the opinion of the radiologist that the lesion has probably 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 probable that this rule will be used for lymph nodes because 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 nonreproducible, 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, which 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 Nontarget Lesions

While some nontarget lesions may be measurable, they should only be assessed qualitatively at the time points specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression).
- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion and/or maintenance of tumor marker level above the normal limits.

- When the participant also has measurable disease: In this setting, to achieve “unequivocal progression” on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely based on changes in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the participant has only non-measurable disease: This circumstance arises in some Phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concept applies 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 nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants 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 (ie, 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 participant 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 (ie, 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 participant’s baseline lesions show PR or CR. 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 study 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 a participant who has visceral disease at baseline and while on study has a CT or MRI of the brain ordered which reveals metastases. The participant’s brain metastases are 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 fluorodeoxyglucose PET (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 for 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 preexisting 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 BOR is the best response recorded from the start of the study drug treatment until the end of treatment considering any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so protocols should be clear if posttreatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant’s BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the BOR.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR 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 participant’s best response depends on the subsequent assessments. For example, a participant 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 participant lost to follow-up after the first SD assessment would be considered not evaluable.

Target Lesions	Nontarget 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

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

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 participants with CR may not have a total sum of “zero” on the eCRF.

In studies where confirmation of response is required, repeated not evaluable (NE) timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants 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 study therapy.

Conditions that define “early progression, early death, and not evaluable” are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine-needle aspirate/biopsy) before assigning a status of CR. 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 (ie, 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 Measure/Duration of Response

Confirmation

In nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified 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 studies. However, in all other circumstances (ie, in randomized studies [Phase 2 or 3] or studies where SD or progression are the primary endpoints), confirmation of response is not required because it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

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

The duration of overall CR is measured from the time measurement criteria 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 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 DSD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The DOR and SD 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 consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between studies are to be made.

16.7. CA-125 Definitions Agreed by Gynecological Cancer Intergroup November 2005

The GCIG has agreed criteria for defining response and progression of ovarian carcinoma which use the serum marker CA-125, and the situations where these criteria should be used. It is recommended that the appropriate definitions described in detail below are cut and pasted into clinical trial protocols. The GCIG requests that data from all trial centers using these definitions is made available to trial centers associated with the GCIG so that continual validation and improvement can be accomplished.

Clinical Situations Where CA-125 Criteria for Response and Progression as Defined Below Are Recommended by the Gynecological Cancer Intergroup

	Use Recommended by GCIG	Not Standard and Needs Further Validation	Not Recommended by GCIG
Front Line Trials	CA-125 Progression		CA-125 Response
Maintenance or Consolidation Trials		CA-125 Response and Progression	
Relapse Trials	CA-125 Response	CA-125 Progression	

Abbreviations: GCIG, Gynecological Cancer Intergroup.

The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA-125 be used in addition to the standard RECIST response criteria.

Evaluation of Response According to CA-125

Definition of response. A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Participants can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the ULN and within 2 weeks prior to starting treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the normal range of CA-125 levels will not interfere with the response definition.
- For each participant, the same assay method must be used, and the assay must be tested in a quality-control scheme.
- Participants are NE by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes 2 treatment modalities for relapse

(eg, surgery and chemotherapy), any CA-125 response results from both treatments modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response rates, an intent-to-treat analysis should be used that includes all participants with an initial CA-125 level of at least twice the ULN as eligible and evaluable. In addition, as a separate analysis, those participants who have both a CA-125 response and whose CA-125 level falls to within the normal range, can be classified as CA-125 complete responders. Participants who have a fall of CA-125 to within the normal range but whose initial CA-125 was less than twice the ULN, have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Evaluation of response according to CA-125 in participants receiving maintenance or consolidation therapy.

Participants whose CA-125 is greater than twice the ULN when they start maintenance or consolidation therapy can be evaluated according to the GCIG CA-125 response definition. It should be noted that there is no data to validate response evaluation in this situation. To prevent the prior therapy interfering with the response assessment the following requirement is recommended. Two pretreatment samples no more than 8 weeks apart are required if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA-125 there must be no more than a 10% fall in CA-125 between the 2 pretreatment samples. The sample closest in time to the test therapy should be considered the pretreatment sample.

Evaluation of response according to CA-125 in participants receiving first-line therapy.

The CA-125 response definition was produced to evaluate relapse therapy. If assessing therapy that includes 2 treatment modalities (eg, surgery and chemotherapy), any CA-125 response is a result of both treatments, and it should be clearly stated that CA-125 cannot distinguish between the effects of the 2 treatments. It should be remembered that for a participant to be classified as a complete responder according to RECIST, tumor marker levels such as CA-125 must be within the normal range.

Evaluation of Best Overall Response in Participants Without Initial Measurable Disease and Evaluable by CA-125

CA-125 may be used to evaluate response in participants without initial measurable disease, either because no measurable disease can be detected or because appropriate scans have not been performed.

CA-125	Nontarget Lesions ^a	New Lesions	Overall Serological Response	Best Response for this Category also Requires
Response and Normalized	CR	No	CR	confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but not response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD ^b	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

^a Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.

^b Unequivocal progression in nontarget lesions may be accepted as disease progression.

Evaluation of Best Overall Response in Participants with Initial Measurable Disease and Evaluable by CA-125

A report that combines both CA-125 and RECIST criteria, is likely to include participants who are measurable by 1 or both of the criteria, who may have events at different time points. In participants who are measurable by both criteria the date of response will be the date of the earlier of the 2 events. The following rules apply when determining the BOR. If participants have PD according to RECIST within 28 days of CA-125 response, they are classified as PD. If the PD according to RECIST is > 28 days before or after the CA-125 response, they are classified as PR. Participants whose best response according to RECIST is SD but who have a CA-125 response are classified as CA-125 responders.

Best Overall Response in Participants with Initial Measurable Disease and Evaluable by CA-125, Combining Both Criteria

Target Lesion ^a	Nontarget ^b	New Lesion	CA-125	Overall Best Response	Best Response for this Category also Requires
CR	CR	No	Normal	CR	confirmed and maintained for at least 28 days
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR not normal	PR	
PR	Non-PD	No	Not PD	PR	
NE	Non-PD	No	PR	PR	
PD or New > 28 days from CA-125 PR ^c			PR	PR	
SD	Non-PD	No	PR	PR	
SD	Non-PD	No	Not PR or PD	SD	
PD or New ≤ 28 days from CA-125 PR*			PR	PD	
PD	Any	Yes or No	Any	PD	
NE	PD	Yes or No	Any	PD	
NE	Any	Yes	Any	PD	
NE	Any	Yes or No	PD	PD	

Abbreviations: CR=complete response; NE = not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

*See text above

^a Target lesions include up to 10 measurable lesions as defined by RECIST.

^b Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST.

^c Participants who have a CA-125 response that occurs more than 28 days from PD according to RECIST are considered a PR according to best response, but PD if the RECIST PD is within 28 days of CA-125 response.

Reporting of Response According to Both RECIST and CA-125 Criteria

Responses should be reported separately for each criterion as shown below:

Criteria:	RECIST	CA-125		Best Overall ^a
		Only	All CA-125 Evaluable ^b	
CR (%)	4 (11.4%) ^c	4 (40.0%) ^d	8 (19.0%) ^d	8 (17.8%)
PR (%)	5 (14.3%)	4 (40.0%)	6 (14.3%)	9 (20.0%)
SD (%)	16 (45.7%)	2 (20.0%)	20 (47.6%)	18 (40.0%)
PD (%)	10 (28.6%)	0 (0.0%)	8 (19.0%)	10 (22.2%)
Unknown (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Evaluable	35 (100.0%)	10 (100.0%)	42 (100.0%)	45 (100.0%)
Non-evaluable	10	3		^e

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

^a Includes all evaluable participants in the study, regardless of method for assessing response (see best overall response table).

^b Includes all participants who are evaluable by CA-125, either alone, or in combination with other evidence of disease.

^c RECIST includes normalization of CA-125 to achieve CR (see best overall response table).

^d Includes all participants who had both a CA-125 response and their CA-125 level falls to within the normal range.

^e This column only includes eligible participants (ie, evaluable by at least 1 of the criteria, therefore cell blank).

Definition of Progression on First-Line Therapy and Recurrence After First-Line Therapy According to CA-125

Progression is defined according to RECIST but can also be based upon serum CA-125 (defined below) but tumor measurements should take precedence over CA-125. If measurable disease is shrinking during treatment, but the CA-125 indicates progression (as defined below) the participant should continue to receive protocol treatment. If measurable disease shows SD but CA-125 indicates progression after a minimum of 3 courses of chemotherapy, protocol treatment should be changed. If the GCIIG definition based on CA-125 is used to define progression after relapse therapy, it should be noted that it has not been validated.

Evaluation of Progression According to CA-125

Progression or Recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125, according to the following criteria:

- a. Participants with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper normal limit on 2 occasions at least 1 week apart or
- b. Participants with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than, or equal to, twice the nadir value on 2 occasions at least 1 week apart or
- c. Participants with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than, or equal to, twice the upper normal limit on 2 occasions at least 1 week apart.

Elevated values must be confirmed by 2 separate measurements obtained at least 1 week apart. CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Participants are NE by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

A participant may be declared to have PD on the basis of either the objective RECIST criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Definition of progression after first-line therapy in ovarian cancer as proposed by the Gynecological Cancer Intergroup

GCIG subcategorized group	RECIST Measurable/non-measurable disease		CA-125
A	Compared with baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) or Any new lesions (measurable or non-measurable) Date PD: date of documentation of increase or new lesions	A N D / O R	CA-125 $\geq 2 \times$ ULN documented on 2 occasions ^a Date of PD: first date of the CA-125 elevation to $\geq 2 \times$ ULN
B	As for A		CA-125 $\geq 2 \times$ nadir value on 2 occasions # Date of PD: first date of the CA-125 elevation to $\geq 2 \times$ nadir value
C	As for A		As for A

Abbreviations: GCIG=Gynecological Cancer Intergroup; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

GCIG groups A, B, & C defined above.

^a Repeat CA-125 any time, but normally not less than 1 week after the first elevated CA-125 level.

CA-125 levels sampled after participants received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA^{4,5}) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days, should not be taken into account.

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205-216.
2. Rustin GJ, Quinn M, Thigpen T, et al. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst. 2004;96(6):487-488.
3. Vergote I, Rustin GJ, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. J Natl Cancer Inst. 2000;92(18):1534-1535.
4. Taylor PT, Haverstick D. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst. 2005;97(2):151.
5. Rustin GJS. Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst. 2005;97(2):152.

16.8. Serum Creatinine Based Equations Used to Estimate Renal Function

The CKD-EPI (2021) equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m² are desired.

Recommend use of calculator found at:

https://www.kidney.org/professionals/kdoqi/gfr_calculator, which corresponds to the equation below.

Expressed as a single equation:

$$eGFR = 142 * \min(\text{standardized } S_{cr}/K, 1)^{\alpha} * \max(\text{standardized } S_{cr}/K, 1)^{-1.200} * 0.9938^{\text{Age}} * 1.012 [\text{if female}]$$

Abbreviations / Units:

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m²

S_{cr} (serum creatinine) = mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (females) or -0.302 (males)

min = indicates the minimum of S_{cr}/K or 1

max = indicates the maximum of S_{cr}/K or 1

Clinical Use:

The Recommended method for estimating GFR in adults from the National Kidney Foundation is the 2021 CKD-EPI equations.

Designed for use with laboratory CRE values that are standardized to IDMS. (See "About GFR" button.)

Estimates GFR from S_{cr} , age and sex

More accurate than the Modification of Diet in Renal Disease Study equation, particularly in people with higher levels of GFR.

The CKD-EPI equation is modeled using least squares linear regression to relate log transformed measured GFR to log-transformed filtration markers, age and sex with two slope splines for CRE.

16.9. Prophylactic Care Recommendations

Optimizing general skin care may be helpful for preventing and limiting reactions. Dry skin often occurs with RAF inhibitor treatment and preventing dry skin is critical.

All participants should be counseled at treatment initiation to adopt gentle skin care practices that involve daily baths and the use of mild cleansers. Limit soap usage only to "essential areas" (face, axillae, groin, between toes).

High-quality hypoallergenic skin moisturizers should be used at least twice a day. A cream- or ointment-based emollient is preferred because lotions are too thin. Emollients are designed to prevent water loss from skin; therefore, "thicker" emollients (anything in a tub-like container) are recommended.

Skin Recommendations for Study Participants

Acneiform dermatitis is common in postpubescent participants. Most reports of acneiform rash arise within the first 2 cycles of treatment and may be preventable. Early onset RAF inhibitor-associated acneiform dermatitis is believed to be associated with disrupted skin barrier and inflammation rather than infection.

At the initiation of BGB-3245 treatment, all study participants are recommended to limit sun exposure and use skin moisturizer, wear hats, and use sunscreen (SPF > 15 UVA and UVB) while on the study drugs, and for 2 months after the last dose. Prophylactic topical clindamycin lotion 1.0% should be applied to the face, and chest. The use of topical steroid cream (not stronger than 1% hydrocortisone) is strongly recommended. Participants may be advised to apply moisturizer and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night. Strategies for preventing acneiform dermatitis in participants should be utilized. In addition, participants should begin prophylactic treatment with tetracyclines (eg, doxycycline or minocycline) 50 mg/day for 3 months.

Reactive approach to acneiform rash. If acneiform rash still develops and is a bother to the participant, add hydrocortisone cream (2.5%) or triamcinolone ointment (0.1%) twice a day. If acneiform rash continues to worsen or if an infection (eg, pustular) is suspected, refer to dermatology; stronger topical steroids or oral retinoids may be added.

Do not use agents with the potential to cause dry skin, such as benzoyl peroxide, salicylic acid, acne skin washes, scrubs, exfoliants, antiaging creams, alcohol (cleansers, wipes) or other agents that can dry skin. Avoid topical retinoids.

Fissured and cracked skin is more likely to lead to a superinfection, which is associated with pain rather than itching. For worsening infectious or noninfectious rash (eg, rash erythematous), please consult your dermatologist.

Diarrhea Recommendation for All Participants

First onset of diarrhea is typically reported during the first 2 cycles of BGB-3245 treatment, with most cases being Grade 1 or Grade 2. For diarrhea, all participants should be counseled at treatment initiation to manage their diet. Initial interventions for Grade 1-2 diarrhea should include avoidance of greasy foods and possible adoption of the BRAT diet. Probiotics can also

be added. If this is insufficient, loperamide or similar antidiarrheal agents can be used per institutional practice. Consider if other newly prescribed medications may be contributing to diarrhea.