CLINICAL STUDY PROTOCOL

Investigational Products: BGB324; Pembrolizumab

Sponsor: BerGenBio ASA
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Protocol Number: **BerGenBio ASA**: BGBC007
Merck & Co: MK-3475 PN-530

Phase: Phase II

Protocol Title: A Phase II, Multi Center Study of BGB324 in combination with Pembrolizumab in Patients with Previously Treated, Locally Advanced and Unresectable or Metastatic Triple Negative Breast Cancer (TNBC) or Triple Negative Inflammatory Breast Cancer (TN-IBC)

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CONFIDENTIAL STATEMENT:

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorization from BerGenBio ASA

Protocol Approval Signatures

Sponsor's Approval:
This study will be conducted in compliance with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

This protocol has been approved by BerGenBio ASA.

Signature: [redacted] **Date**: 27 June 2017

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Investigator's Approval:

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described and will complete the study within the time designated. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical, and clinical experience when available e.g. in updated editions of the Investigator's Brochure (IB), to all staff in my unit involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with medical treatment and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of patients. All patients will be informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. They will be informed that they may withdraw from the study at any time. I will use only the consent and information form approved by BerGenBio ASA (BerGenBio) and the Ethics Committee (EC) for this study. I will supply BerGenBio with any material written by myself e.g. summary of study, which is given to the EC in support of the application.

Where applicable, the patient information contained in clinic records, reports and manuscripts will be transcribed to the case report forms (the case report form may be the original source document for specified items). Either I or an appointed person will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report form. I agree to the audit and monitoring procedures that involve verification of such study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed, from the hospital or institution where the study was conducted.

I understand that the case report forms and other data pertinent to this study are the property of BerGenBio and are confidential. I will supply BerGenBio (or their delegates) with the study data in such a way that the patient cannot be personally identified.

Investigator:_____ _____

Signature Date

Print Name:_____

Institution Name:_____

Institution Address:_____

OTHER CONTACT INFORMATION

Full contact details for each Investigational site, the Sponsor (including medical out-of-hours contact number), and key coordinating and operational personnel will be maintained in the Trial Master File (TMF) and in each Site Study File.

PROTOCOL SYNOPSIS

Protocol No: BGB324 BGBC007 / MK-3475 PN-530

Study Title: A Phase II Multi Center Study of BGB324 in combination with Pembrolizumab in Patients with Previously Treated, Locally Advanced and Unresectable or Metastatic Triple Negative Breast Cancer (TNBC) or Triple Negative Inflammatory Breast Cancer (TN-IBC)

Investigational Products:

- BGB324: a potent selective small molecule inhibitor of Axl, a surface membrane protein kinase receptor.
- Pembrolizumab: humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein.

Phase of Development: Phase II

Number of Sites: Up to approximately 20 sites. Additional sites may be added as required to meet the enrolment needs of the clinical trial.

Number of Patients:

Up to 56 evaluable patients will be enrolled into the study. Approximately 75 patients will be screened in order to identify up to 56 patients who meet all the inclusion and exclusion criteria and are evaluable for response. This assumes a 25% screen failure rate, given the need for patients to provide a fresh tissue biopsy sample.

Study Objectives and Endpoints

Table 1: Study Objectives and Endpoint (Assessment)

Objective	Endpoint (Assessment)
Primary:	
• To assess anti-tumor activity of the combination of BGB324 and pembrolizumab	• Objective response rate (complete response and partial response)
Secondary:	
• To assess the safety of BGB324 and pembrolizumab when given in combination	• The number and frequency of adverse events; assessment of safety laboratory parameters, vital signs and ECGs
• To further assess the anti-tumor activity of the combination of BGB324 and pembrolizumab	• To include Disease Control Rate, Duration of Response; Progression-free Survival; 12-month Overall Survival
• To evaluate the pharmacokinetic profile of BGB324 when given with pembrolizumab.	• Assessment of pharmacokinetic variables including C_{max}, AUC, $t_{½}$
Exploratory:	
• To assess relevant biomarkers	• To assess PD-L1 and Axl expression in patients with TNBC and TN-IBC • To assess any correlation or association between expression level of PD-L1 and Axl and anti-tumor outcomes such as ORR • Assessment of relevant biomarkers in tumor and blood which support immune modulation and Axl signalling

Study Design

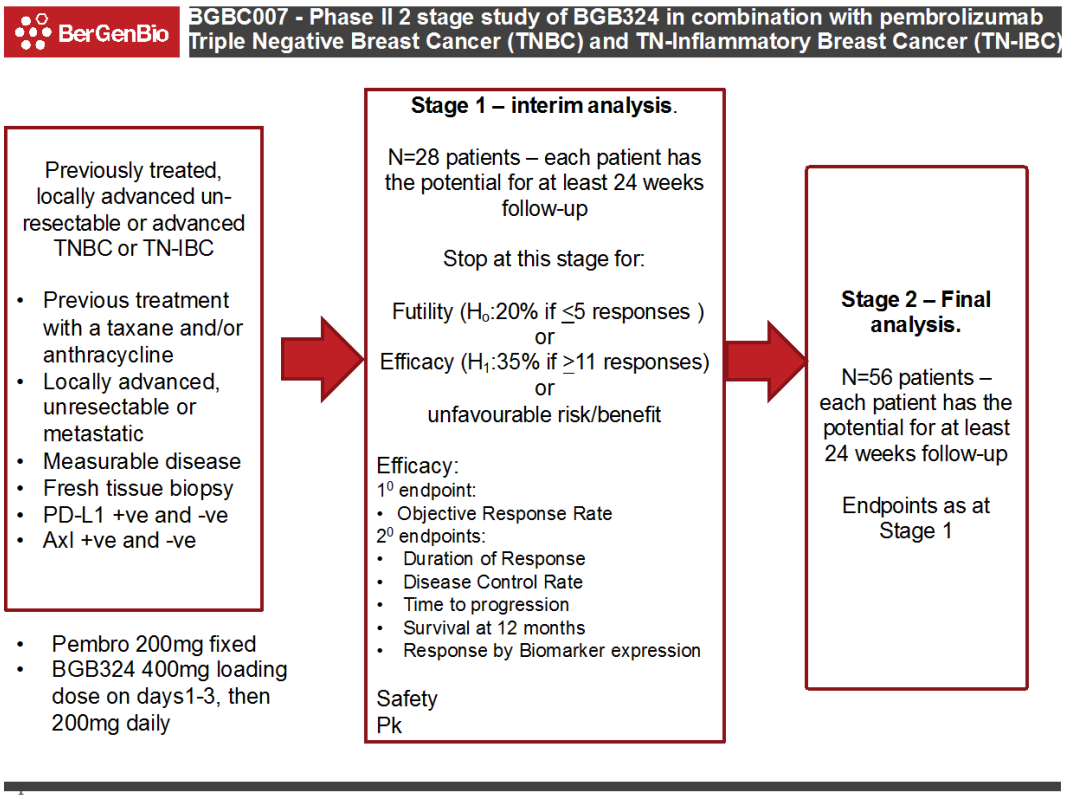
This is an open-label, single arm, multi-center phase II study to assess the anti-tumor activity and safety of BGB324 in combination with pembrolizumab in patients with previously treated, locally advanced and unresectable, or metastatic TNBC or TN-IBC.

Pembrolizumab has not previously been combined with BGB324 in patients (in any indication) and therefore, a safety run-in will include a total of 12 patients. The internal Data Review Committee (DRC) will conduct a review of the safety data from the first 6 patients who have had the potential to be followed for at least 6 weeks (minimum 2 cycles), and then again after a further 6 patients (12 patients in total) have had the potential to be followed for at least 6 weeks. The DRC will consider the emerging safety profile, together with the number of patients requiring a BGB324 dose reduction and the number of patients requiring either BGB324 or pembrolizumab or both to be permanently discontinued. The DRC will consider whether a revised BGB324 dose (dose level -1) is appropriate for new patients entering the study.

The study will utilize a 2-stage, single arm, extension of Simon's 2-stage design[1] with one (efficacy) interim and a final analysis. The interim analysis will be conducted when 28 patients are evaluable for Objective Response Rate (ORR). If 5 or fewer responses are observed in up to 28 patients, the trial will be terminated in favor of the null for futility. If 11 or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Where 6 to 10 patients have an observed response at the interim analysis, up to a further 28 patients may be evaluated, for a total of 56 patients (Section 8.1) taking the overall risk: benefit of the combination into consideration. A schematic diagram of the study design is provided in Figure 1.

Recruitment to the study will be halted once 28 evaluable patients have been entered and whilst the Stage 1 interim analysis is conducted. Recruitment will recommence if the decision is made to continue to the maximum of 56 evaluable patients.

Figure 1: Schematic diagram of the study design



BGB324 will be administered orally once daily. On the first 3 days of administration, the BGB324 dose will be a 'loading' dose of 400 mg on Days 1, 2 and 3. From Day 4 onwards, patients will receive a dose of 200 mg daily. If the DRC recommend dose level -1 for new patients (after or during the safety run-in), the dose of BGB324 will reduce to a loading dose of 200 mg on Days 1, 2 and 3 and to 100 mg from Day 4 onwards.

A fixed dose of 200 mg pembrolizumab will be given by intravenous (i.v.) infusion over 30 minutes every 3 weeks in all patients. The 3-weekly pembrolizumab dosing schedule will be used to define 3-week treatment cycles throughout the treatment period of the study.

The BGB324 and pembrolizumab dose levels selected for this study are summarized in Table 2.

Table 2: BGB324 and pembrolizumab dosing

BGB324:	Loading Dose: Days 1, 2 & 3	Daily Dose: Day 4 onwards	Frequency	Route of administration
Dose level	400 mg	200 mg	Daily	Oral
Dose level -1	200 mg	100 mg	Daily	Oral
Pembrolizumab	**Dose**	**Regimen**	**Frequency**	**Route of administration**
	200 mg	Day 1 of each cycle	Every 3 weeks	IV

Dosing of both drugs will commence on Day 1. On days when both BGB324 and pembrolizumab are given, pembrolizumab will be given first and patients will be observed for 1 hour for infusion and other adverse events (AEs). BGB324 may then be administered.

BGB324 and pembrolizumab will be given until disease progression (note that in the absence of clinical deterioration, treatment can continue and clinical progression should be confirmed after 4 weeks) or until an unacceptable toxicity has occurred which necessitates treatment withdrawal (Section 6.6), or until 106 weeks (35 cycles), equivalent to 24 calendar months.

Patients who discontinue BGB324 treatment (for reasons other than disease progression) may be able to continue with (monotherapy) pembrolizumab until 106 weeks (that is, 35 completed cycles of pembrolizumab, equivalent to 24 calendar months).

Patients who discontinue pembrolizumab (for reasons other than disease progression) may be able to continue with BGB324 for up to 106 weeks (equivalent of 24 calendar months).

If a tumor imaging assessment is suggestive of progressive disease, but the patient has an absence of clinical deterioration, a confirmatory scan after 4 weeks (this may be an unscheduled scan) will be made in order to rule out a pseudo or false progression caused by an inflammatory immune response. In the absence of clinical deterioration, treatment with both BGB324 and pembrolizumab can continue until disease progression is confirmed.

As per RECIST 1.1[2], all patients who are considered to have a complete or partial response must have this response confirmed by a confirmatory scan at least 4 weeks later.

A DRC, consisting of Principal Investigators, the Sponsor's Medical Monitor, at least one representative from both the Sponsor and Merck, and invited experts as required, will review all patient safety data after 6 patients have been enrolled and followed up for 6 weeks (2 cycles), and then again after an additional 6 patients (total 12 patients) have had the potential to be followed for 6 weeks. At each of these safety reviews, the DRC will consider the rate of BGB324 dose reductions and the rate of permanent discontinuation from BGB324 and pembrolizumab. The DRC will consider if a revised dose (dose level -1) for BGB324 is appropriate.

Additionally, a review of emerging safety data from the whole BGB324 program will be made 6-monthly.

The Sponsor may request ad-hoc DRC meetings at any time during the study to assess interim

safety data and review the need for dose modifications. For more details on the dose modification rules for BGB324 and pembrolizumab, please refer to Section 6.6.1 and Section 6.6.2.

Study Procedures and Assessments

Please refer to Schedule of Study Assessment Table 4 and Table 5 for full details of all study assessments. For patients who have stopped BGB324, but continue with monotherapy pembrolizumab, there will be an adjusted list of study assessments.

The study will consist of a Screening period, Treatment period (made up of consecutive, 3-week cycles), a Post Treatment Visit, and Follow-up Assessments. Patients must provide informed consent prior to commencing the study screening procedures. All patients are required to have a fresh (newly acquired) tumor biopsy taken at Screening, and are required to provide sufficient tumor specimens to enable both Axl kinase and PD-L1 expression to be measured.

Tumor specimens are therefore to be submitted in sufficient quantity to allow for PD-L1 immunohistochemistry (IHC) and Axl IHC analysis (see the Pathology Manual). Samples with limited tumor content (<100 viable tumor cells), cytology, cell block, decalcified or formalin fixed but previously frozen, frozen sample, plastic embedded, bone, bone marrow, clot and fine needle aspirates are inadequate for defining tumor PD-L1 and Axl status.

Axl expression can only be obtained from a fresh (newly acquired) tumor tissue sample. PD-L1 expression can be determined from either a fresh (newly acquired) or archival sample. In all cases, the tumor tissue must not have been previously irradiated.

Different testing laboratories will be used for Axl kinase and PD-L1 expression.

The fresh (newly acquired) tumor tissue sample will be either newly obtained core needle biopsy (minimum gauge 18) or a newly obtained excisional biopsy.

The following tumor tissue options are available (all options require fresh tumor tissue sample, however, if there's insufficient fresh tumor tissue available, the 3rd option below allows the submission of archival tissue in addition to the fresh tissue sample):

- Where only a core needle biopsy is used, a minimum of 4 core biopsy samples are required. These should be placed in formalin and processed into 2 single paraffin embedded (FFPE) blocks (2 cores in one block and 2 cores in the other block) within 24-48 hours.
- Alternatively, where only a newly obtained excisional biopsy sample is used, this biopsy should be processed into 2 paraffin embedded (FFPE) blocks within 24-48 hours.
- Alternatively, 2 core needle (fresh tumor) biopsies or a single newly obtained excisional biopsy sample can be submitted (processed into one FFPE block), together with either an archival (FFPE) tumor tissue block or a minimum of 10 unstained slides each 5µm cut from the archival tumor sample block. The unstained slides must arrive at the testing laboratory within 14 days. In this option, an archival FFPE block is strongly preferred over unstained slides cut from an archival FFPE block.

Archival blocks must be clearly labelled as archival.

Slides cut from an archival tissue block must be clearly marked as having come from an archival block.

Finally, where patients also have (additional) archived biopsy material which is suitable for additional (such as exploratory) biomarker assessment a sample of this material (either as an archival FFPE block or slides cut (and paraffin dipped) from the archival block) can also be prepared for study biomarker assessment. The patient will be offered a separate optional patient consent to enable this 'archival biomarker tumor sample' to be submitted.

The first dose of study drug must be administered within 4 weeks of commencing the Screening assessments. Tumor imaging by computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis is required during the Screening period. X-ray scans can be used where appropriate (for example, for symptomatic sites that are negative on a bone scan). All patients should undergo a bone scan and a brain scan in the 6 weeks prior to starting treatment.

Recording of AEs and concomitant medications, plus laboratory screens including electrocardiographs (ECGs) will be performed at each study visit. During Cycle 1, patients will have study visits on Days 1, 2, 3 and 4, then on Days 8 and 15. From Cycle 2, Day 1, study visits will be reduced to every 3 weeks.

ECG assessments will be performed in triplicate at pre-dose and 6 hours after the BGB324 dose on Day 1, Cycle 1 and then repeated pre-BGB324 dose on Days 2, 3 and 4 (Cycle 1) and then at every visit thereafter.

Further tumor imaging will be performed in all patients every 9 weeks for the first 46 weeks and then 12-weekly thereafter until progression (which may be confirmed). On each occasion, tumor assessments will include imaging of the chest, abdomen and pelvis. Additional anatomy, including brain and bone, should be imaged based on signs and symptoms of individual patients. Disease response will be evaluated at these time points according to RECIST 1.1[2]. If either or both of the study treatments are stopped for any reason other than confirmed progression, tumor imaging will continue every 12 weeks until confirmed progression.

Patients who are suspected of having a complete or partial response will have their response confirmed at the next scheduled assessment or no earlier than 4 weeks (28 days) later.

Blood sampling for PBMC and Axl signaling and inhibition biomarker analysis will be performed at Screening, Cycle 1, Days 4 and 8 and every study visit thereafter until Cycle 9, Day 1.

Blood sampling for BGB324 pharmacokinetic (PK) analysis will be performed on blood samples taken on:

- Cycle 1, Days 1 and 3 as follows: pre-dose and at 2, 4, 6 and 8 hours post dose;
- Cycle 1, pre-dose on Days 2, 4, 8 and 15;
- Cycles 2 and 3, pre-dose (study days 22 and 43 respectively).

Blood sampling for future pembrolizumab PK analysis will be performed on blood samples taken pre-dose on Cycle 1, Days 1 to 4, 8 and 15 and then pre-dose at Cycles 2 and 3 (study days

22 and 43 respectively). These samples will be frozen and stored centrally for future reference and analysis.

Patients with tumor amenable to repeat sampling may have additional fresh biopsies taken on up to 2 occasions post-dose at time points agreed between the Investigator and the patient. Where possible, efforts will be made to obtain follow up biopsy material where a patient has responded to treatment or has progressed on treatment.

Further details on sample collection and handling for all PK and biomarker assessments are described in the Laboratory Manual.

Patients who discontinue BGB324 treatment (for reasons other than disease progression) may be able to continue with (monotherapy) pembrolizumab until 106 weeks (that is, 35 completed cycles of pembrolizumab). These patients will no longer be required to have the following assessments from 6 weeks after the discontinuation of BGB324 (unless clinically indicated):

- ECG;
- Echocardiogram (or Multi Gated Acquisition Scan (MUGA));
- Optional tumor biopsy (for example at subsequent progression);
- Biomarker sampling.

The Post Treatment Visit will occur 30 days after the patient has discontinued both treatments on study. Patients who withdraw from either or both study treatments prior to disease progression will continue to have tumor imaging assessments every 12 weeks until disease progression is documented (and confirmed, if necessary). The date of disease progression will be captured.

Subsequent to disease progression (confirmed if necessary), patients will continue to have their survival status checked every 12 weeks until death or the Last Patient Last Visit (LPLV) date (see Section 8.6), whichever is earlier. Survival status can be checked via telephone.

Inclusion/Exclusion Criteria

Inclusion Criteria

A patient will be suitable to proceed to treatment on study if they meet all of the following criteria:

1. Provision of signed informed consent.
2. Male and non-pregnant females who are aged 18 years or older at the time of provision of informed consent.
3. Histopathologically or cytologically documented TNBC or TN-IBC. Tumors must have been confirmed negative for ER and PR by IHC (<1% positive tumor nuclei, as per ASCO-CAP guideline recommendations[3]) and negative for HER2 by IHC or fluorescent or chromogenic in situ hybridization (FISH or CISH). Patients with equivocal HER2 results by IHC should have their negativity status confirmed by FISH.
4. Locally advanced and unresectable or metastatic TNBC or triple negative inflammatory breast cancer.
5. Received one or more prior therapies for TNBC or inflammatory breast cancer in the metastatic setting, and prior treatment (metastatic or (neo) adjuvant) must have

included a prior taxane and/or anthracycline-based therapy

6. Has measurable disease as defined by RECIST 1.1[2] on computed tomography (CT) or magnetic resonance imaging (MRI) and as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Provision of suitable tumor tissue for the analysis of Axl kinase expression and PD-L1 expression. Suitable tumor tissue must consist of a minimum of newly acquired (fresh) tumor tissue sample (as a FFPE block), together with either further newly acquired tumor tissue (i.e. further FFPE block) or an archival tumor tissue sample (as a further FFPE block or further 10 unstained slides). See Section 5.3.13 for further details.
8. Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1 [Appendix A].
9. Life expectancy of at least 3 months.
10. Adequate organ function confirmed at Screening and within 10 days of initiating treatment, as evidenced by:
    a. Platelet count ≥100,000 /mm^3;
    b. Hemoglobin ≥9.0 g/dL (≥5.6 mmol/L);
    c. Absolute neutrophil count (ANC) >1,500 /mm^3;
    d. Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN), or ≤5 times the ULN for patients with liver metastases;
    e. Total bilirubin ≤1.5 times the ULN, or direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN;
    f. Creatinine ≤1.5 times the ULN and calculated creatinine clearance >60 mL/min (by Cockcroft Gault formula; see Appendix B);
    g. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 times the ULN and Activated Partial Thromboplastin Time (aPTT) ≤1.5 times the ULN. *Note: If patient is receiving anticoagulant therapy, then PT or PTT must be within therapeutic range of intended use of anticoagulants*;
    h. LDH ≤2.5 times the ULN.
11. Female patients of childbearing potential must have a negative pregnancy test (either urine or serum pregnancy test) within 72 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the patient received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
13. Patients of reproductive potential must be willing to practice highly effective methods of contraception (such as those described in Section 6.14) throughout the study and for 120 days after the last dose of study medication. Abstinence is acceptable if this is the usual lifestyle of the patient. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility or evidence of post-menopausal status defined as any of the following:

a. ≥45 years of age and has not had menses for more than 1 year;
b. Amenorrheic for >2 years without a hysterectomy and oophorectomy and a follicle stimulating hormone (FSH) value in the postmenopausal range upon Screening evaluation and oestradiol <30 pg/mL;
c. Post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.

Exclusion Criteria

A patient will not be suitable to proceed to treatment on study if they meet any of the following criteria:

1. Has disease that is suitable for local therapy administered with curative intent.
2. More than 3 previous lines of therapy in the metastatic setting.
3. Has received prior therapy with an immunomodulatory agent.
4. Has a known additional malignancy that is progressing or requires active treatment. *Note: Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.*
5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. *Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks prior to the first dose of trial treatment and any neurological symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment*.
6. History of the following cardiac conditions:
   a. Congestive cardiac failure of >Grade II severity according to the NYHA (Appendix C: defined as symptomatic at less than ordinary levels of activity);
   b. Ischemic cardiac event including myocardial infarction within 3 months prior to first dose;
   c. Uncontrolled cardiac disease, including unstable angina, uncontrolled hypertension (i.e. sustained systolic BP >160 mmHg or diastolic BP >90 mmHg), or need to change medication due to lack of disease control within 6 weeks prior to the provision of consent;
   d. History or presence of sustained bradycardia (≤55 BPM), left bundle branch block, cardiac pacemaker or ventricular arrhythmia. *Note: Patients with a supraventricular arrhythmia requiring medical treatment, but with a normal ventricular rate are eligible*;
   e. Family history of long QTc syndrome; personal history of long QTc syndrome or previous drug-induced QTc prolongation of at least Grade 3 (QTc >500 ms).
7. Abnormal left ventricular ejection fraction on echocardiography or MUGA (less than the lower limit of normal for a patient of that age at the treating institution or <45%, whichever is lower).

8. Current treatment with any agent known to cause Torsades de Pointes which cannot be discontinued at least five half-lives or two weeks prior to the first dose of study treatment.
9. Screening 12-lead ECG with a measurable QTc interval according to Fridericia's correction >450 ms.
10. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study treatment.
11. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to a previously administered agent. *Note: Patients with ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study.*
12. Received an anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of study treatment or who has not recovered (i.e. ≤Grade 1 or baseline) from AEs due to agents administered more than 4 weeks earlier.
13. Major surgery within 28 days prior to start of study treatment and failure to have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study treatment. *Note: Major surgery does not include procedures for insertion of venous catheters or biopsies*.
14. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoetin) within 4 weeks prior to the first dose of study treatment. *Note: Patients receiving stable dose of growth factors with a hemaglobin value that meets Inclusion Criterion 10b may be included.*
15. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
16. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). *Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.*
17. Known history of human immunodeficiency virus (HIV 1/2 antibodies)
18. Has known active infection with Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA (qualitative) is detected). *Note: i) Patients with a history of hepatitis B infection are eligible provided they are hepatitis B surface antigen negative ii) Patients with a history of hepatitis C infection are eligible provided they have no evidence of hepatitis C RNA using a qPCR at least 6 months after completing treatment for hepatitis C infection.*
19. Has received a live-virus vaccination within 30 days of planned treatment start. *Note: Seasonal flu vaccines that do not contain live virus are permitted.*
20. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
21. Has a history of interstitial lung disease.
22. Inability to swallow or tolerate oral medication.

23. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohn's disease, or previous bowel resection which is considered to be clinically significant or could interfere with absorption.
24. Known lactose intolerance.
25. Requires vitamin K antagonists. *Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included. Factor Xa antagonists are permitted.*
26. Treatment with any of the following: histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 7 days of start of study treatment.
27. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index.
28. Known severe hypersensitivity (≥Grade 3) to BGB324, pembrolizumab, and/or any of their excipients.
29. Has an active infection requiring systemic therapy (apart from cutaneous infections).
30. Has a history or current evidence of any condition, therapy, or laboratory abnormality that, in the opinion of the Investigator, might confound the results of the trial, interfere with the patient's participation and compliance in the trial, or means it is not in the best interests of the patient to participate.
31. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting from Screening through to 120 days after the last dose of study treatment.
32. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

Statistical Methods and Sample Size

The trial will follow a *k*-stage single arm design with *k*=2, being an extension of Simon's 2-stage design[1]. In this design with *k*=2, there are two analyses: a single interim and a final analysis. At the interim, the response rate is evaluated in a fixed number (*m*) of patients using a predefined decision rule to determine if the study should stop for futility (in the situation where the null is confirmed) or for efficacy (in the situation where the alternative hypothesis is confirmed). If neither hypothesis is confirmed, a further fixed number of patients (*l*) are assessed for response and a final analysis is performed on all (*m*+*l*) patients. In both interim and final analyses, the response rate will be presented together with the associated exact 90% confidence interval (CI).

The rationale for a null hypothesis of p_0=0.20 is based on previously published[10] analysis from a clinical trial with pembrolizumab (KEYNOTE-012) in 32 patients with metastatic TNBC (27 patients were evaluable), where an ORR of 18.5% has been observed for pembrolizumab monotherapy. These patients were relatively heavily pre-treated PD-L1 positive patients, with over 50% having received 3 or more lines of therapy.

The ORR of pembrolizumab in combination with BGB324 is expected to be at least as high as this in patients unselected for PD-L1 positive disease.

With p_0=0.20 and p_1=0.35, the interim will be conducted with *m*=28 evaluable patients who have the potential for at least 24 weeks (that is, at least 2 on treatment scans) of follow-up. If 5 or fewer responses are observed in up to 28 patients, the trial will be terminated in favor of the null

for futility; however, if 11 or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Otherwise, up to a further 28 patients may be evaluated, for a maximum total of 56 evaluable patients. The full study population will have the potential for at least 24 weeks of follow-up. If a total of 17 or more responses are seen in up to 56 patients, then the null will have been rejected in favor of the alternative; otherwise the null will not have been rejected.

Up to 56 evaluable patients may therefore be enrolled to this clinical trial. It is expected that approximately 75 patients will be screened in order to identify 56 patients who meet all the inclusion and exclusion criteria and who are evaluable for response.

An evaluable patient is defined as one who has received at least one dose of pembrolizumab and BGB324, and has measurable disease, as determined by the investigator site at baseline.

Demographic and clinical characteristics at entry will be summarized using appropriate descriptive statistics. PD-L1 and Axl expression will be summarized.

Further details on the statistical methods and sample size can be found in Section 8.1.

Schedules of Assessment and Pembrolizumab Administration Timing

Table 3 summarizes the timing of pembrolizumab administration up to cycle 35 (approximately 24 months of treatment) in relation to the timing of disease assessment.

Table 4 summarizes the schedule of assessments in Year 1 and **Table 5** summarizes the schedule of assessments in Year 2.

Table 3: Pembrolizumab 3 weekly schedule and disease assessment timings

Year 1, First 6 months*									
Week Number:	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**
Start of month:	**1**				**4**				**7**
Pembrolizumab cycle:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Disease Assessment / Scan (+/- 7 days):	Scanned at screening			X			X		
Year 1, Second 6 months*									
Week Number:	**28**	**31**	**34**	**37**	**40**	**43**	**46**	**49**	**52**
Start of month:				**10**				**13**	
Pembrolizumab cycle:	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Disease Assessment / Scan (+/- 7 days):	X			X			X		
Year 2, First 6 months*									
Week Number:	**55**	**58**	**61**	**64**	**67**	**70**	**73**	**76**	**79**
Start of month:			**16**				**19**		
Pembrolizumab cycle:	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Disease Assessment / Scan (+/- 7 days):		X				X			
Year 2, Second 6 months*									
Week Number:	**82**	**85**	**88**	**91**	**94**	**97**	**100**	**103**	**106**
Start of month:		**22**				**25**			
Pembrolizumab cycle:	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**Stop**
Disease Assessment / Scan	X				X				X

(+/- 7 days):									

*A month is 4 weeks (not a calendar month).

Table 4: Schedule of Study Assessments – Year 1

	Screening	Cycle 1 (21-d cycle)						Cycle Number – Year 1																Post Treatment Visit[14]	Follow Up[15]
								2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
Day	Up to -28	1	2	3	4	8	15	22	43	64	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	1[13]	+30 from last dose	
Start of Week # (+/- 3 days)	-4 weeks to 0	1				2	3	4	7	10	13	16	19	22	25	28	31	34	37	40	43	46	49		
Demographics[17]	X																								
Medical history	X																								
Inclusion/exclusion checks	X																								
Pregnancy or FSH test[1]	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[4]	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X				X	X	X																X	
Thyroid function tests[5]	X								X		X		X		X		X		X		X		X	X	
Echocardiogram (or MUGA)[16]	X														X								X		
ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor imaging[7]	X									X			X			X			X			X		(X)	(X)
Disease Assessment[7]	X									X			X			X			X			X		(X)	(X)
Tumor (fresh tissue) biopsy[8]	X	(X: up to 2 optional post treatment biopsies)																							
Tumor (archival)[8]	(X)																								
Biomarkers[9]	X	(X)			X	X		X	X	X	X	X	X	X	X										
Pembrolizumab dosing[10]		X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BGB324 dosing[11]		X – consecutive daily dosing in 21-d cycles																							
PK sampling (BGB324)[12]		X	X	X	X	X	X	X	X																
PK sampling (pembrolizumab)[12]		X	X	X	X	X	X	X	X																
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Subsequent anti-cancer treatment																									X
Survival Follow Up[15]																									X

Table 5: Schedule of Study Assessments - Year 2

	Cycle Number – Year 2																		Post Treatment Visit[14]	Follow Up[15]
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35		
Day	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	1^{13}	+30 from last dose	
Week Number (+/- 3 days)	52	55	58	61	64	67	70	73	76	79	82	85	88	91	94	97	100	103		
Pregnancy test[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis																			X	
Thyroid function tests[5]		X		X		X		X		X		X		X		X		X	X	
Echocardiogram (or MUGA)[16]								X								X				
ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor imaging[7]			X				X				X				X				(X)	(X)
Disease Assessment[7]			X				X				X				X				(X)	(X)
Tumor (fresh tissue) biopsy[8]	(X: up to 2 optional post treatment biopsies)																			
Pembrolizumab dosing[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
BGB324 dosing [11]	X – consecutive daily dosing in 21-d cycles																			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Subsequent anti-cancer treatment																				X
Survival Follow Up[15]																				X

General instructions:

- Informed Consent must be obtained using the current version of the PIS/ICF prior to commencing Screening.
- From C2 onwards a tolerance window of +/-3 days is permitted. Other tolerance windows for specific study assessments are described in the footnotes below.
- On dosing days, assessments should be performed prior to dosing unless specified otherwise.
- (X) denotes an optional sample; or a sample which is not taken at every cycle; or the particular assessment is 'if applicable'; X denotes a study visit with multiple samples. Please refer to Footnotes.
- Additional assessments may be carried out at any point in the study where clinically indicated.

Footnotes:

1 A pregnancy test is required within 3 days prior to C1D1. A negative pregnancy test may be confirmed by urine or blood test. Where a urine test is positive or equivocal, a blood test must be performed to confirm the result. Patients requiring confirmation of post-menopausal status will have FSH and oestradiol levels assessed at Screening. Where applicable, and in accordance with local regulations, a pregnancy test should be conducted at each cycle (or monthly).

2 Vital signs will include temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate. On pembrolizumab dosing days, vital signs will be taken both pre-dose and at the end of infusion.

3 Physical examination includes height at Screening and weight at Screening and the start of each cycle. After Screening, further assessments may be symptom-directed.

4 Coagulation parameters may be assessed from the Hematology sample.

5 Thyroid function testing may be assessed from the Clinical chemistry sample.

6 For each ECG assessment, triplicate 12-lead ECGs must be taken less than 5 minutes apart, with the patient having rested for at least 10 minutes in the supine position prior to assessment. Time points are relative to BGB324 dosing: C1 D1 pre-dose and 6 hours after dose; D2 pre-dose; D3 pre-dose; D4 pre-dose. All other time-points are pre-dose unless clinically indicated. If a patient permanently discontinues BGB324 (but continues pembrolizumab), the last ECG will be performed at the next pembrolizumab administration. If a patient has BGB324 interrupted for 14 days for toxicity or QTC prolongation, an ECG will be conducted twice weekly for the following 2 weeks once a patient restarts BGB324 daily dosing.

7 Tumor imaging will be performed at Screening, then every 9 weeks for the first 46 weeks, and then every 12 weeks thereafter (+/- 7 days). A tumor response or disease progression should be confirmed no less than 28 days after the initial finding. If treatment administration is misaligned with weeks (e.g. because of treatment delay), the tumor imaging schedule should be maintained by week number and continue if necessary. The schedule of disease assessments is every 12 weeks once a patient has stopped (one or both study treatments) or completed their treatment in the absence of progression. These may continue into Follow Up.

8 Fresh tumor tissue from all patients at Screening is mandatory, and optional at up to 2 time points during participation in the clinical trial ('on-study' biopsy). Where possible, these optional samples should be taken at the point of tumor response or progression. Suitable archival biopsy material may also be obtained at Screening. Please refer to protocol Section 5.3.13, the Laboratory or Pathology Manual for full details on biopsy sample collection, time-points, processing, storage and shipment. If a patient discontinues BGB324 (but continues pembrolizumab), there is no requirement for the optional 'on study' biopsy.

9 Blood samples will be collected at Screening (or D1 pre-dose), D4, D8, then at every study visit up to and including C9 D1 to prepare PBMC and serum samples for Axl signaling and inhibition biomarker assessment. Please refer to the Laboratory Manual for full details on biomarker sample collection, time-points, processing, storage and shipment. If a patient discontinues BGB324 (but continues pembrolizumab), there is no requirement for biomarker blood samples.

10 Pembrolizumab dose of 200 mg will be administered every 3 weeks (timing window +/- 3 days). Each dose will be infused over 30 minutes (timing window -5/+10 minutes)

11 BGB324 will be taken orally once daily. On visits when pembrolizumab and BGB324 are given on the same day, pembrolizumab must be given first and the patient observed for 1 h prior to administration of BGB324.

12 a) The maximum PK sampling time points for the measurement of BGB324 in blood will be: C1 D1 pre-dose, 2, 4, 6, 8 hours ; D2 pre-dose; D3 pre-dose, 2, 4, 6, 8 hours; D4 pre-dose; and then pre-dose at C1D8, C1D15, C2D1 and then C3D1. Samples should be taken contemporaneously with the ECG assessments on C1 D1-4. All sample times are approximate but every effort must be made to take PK samples at specified times.

b) The maximum PK sampling time points for the measurement of pembrolizumab in blood will be: C1 D1 pre-dose; D2; D3; D4; and then at C1D8, C1D15; C2D1 pre-pembro dose and then C3D1 pre-pembro dose. All sample times are approximate but every effort must be made to take PK samples at specified times

c) All sample times are approximate and every effort must be made to take PK samples at specified times. Actual sampling times must be recorded in order to assess result relative to BGB324 or pembrolizumab dose. Please refer to the local Laboratory Manual for full details on PK sample collection, time-points, processing, storage and shipment.

13 D1 of next cycle would be "D22" of the previous cycle.

14 A Post Treatment Visit is to be conducted up to 30 days (+/-3 days) from last dose of study drugs. Adverse events and concomitant medications must be assessed to 30 days. Some AEs must be assessed for longer (see Section 7.4.3 and Section 7.5). Other assessments may be carried out between 7-30 days from last dose. Tumor imaging and disease assessment is only required where is part of next scheduled assessment (where patient has not yet progressed) or to confirm response or progression.

15 Tumor imaging and disease assessment will continue every 12 weeks from the last dose of study drug where the patient has not yet progressed or to confirm response or progression. An assessment of disease status, survival status and details of any anti-cancer therapies received after last dose of study drug will also be collected. Survival status (every 12 weeks) can be collected by telephone.

16 Echocardiogram (or MUGA) will be conducted every 6 months whilst a patient receives BGB324. If a patient discontinues BGB324 (but continues pembrolizumab), a final echocardiogram (or MUGA) will be conducted only if one is scheduled in the following 6 weeks.

17 Demography – race, ethnicity, gender, age (birth month and year).

18 Hematology and Clinical Chemistry to be assessed at a suitable time prior to administration of study treatment(s).

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LIST OF ABBREVIATIONS

AE	Adverse event
ALK	anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-24h}	AUC from time zero to 24 hours
AUC_{0-48h}	AUC from time zero to 48 hours
AUC_{0-T}	AUC from time zero to time t
BP	Blood pressure
BPM	Beats per minute
C_{av}	average concentration
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum concentration achieved
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DCR	Disease control rate
DLT	Dose limiting toxicity
DoR	Duration of response
DSUR	Development Safety Update Report
EC	European Community
EC	Ethics committee
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
EU	European Union

FDA	Food and Drug Administration
FPI	First patient in
FPPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
FT3	Free Triidothyromine
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HCV	Hepatitis C virus
hERG	Human ether-à-go-go related gene
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
hr	Hour
i.v.	Intravenous(ly)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IUD	Intrauterine device
LPLV	Last patient, last visit
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi Gated Acquisition Scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell(s)
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PIS	Patient information sheet
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial Thromboplastin Time

Q2W	(dose) every 2 weeks
Q3W	(dose) every 3 weeks
Qd	(dose) daily
qPCR	quantitative polymerase chain reaction
QTc	QT interval corrected for heart rate
QTcF	QT interval utilizing Fridericia's correction
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RTK	receptor tyrosine kinases
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SmPC	summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Elimination half-life
T3	Triiodothyromine
TL	Target lesion
t_{max}	Time to maximum concentration
TMF	Trial Master File
TPS	tumor proportion score
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States (of America)
DRC	Data Review Committee
TNBC	Triple negative breast cancer
TN-IBC	Triple negative inflammatory breast cancer
FISH	Fluorescent in situ hybridization
CISH	Chromogenic in situ hybridization
LDH	Lactate Dehydrogenase
EDC	Electronic Data collection
PD	Progression of disease
CrCl	Creatinine clearance

1 INTRODUCTION

This is an open-label, Multi-Center, Phase II, Simon 2-stage design[1] study of the anti-tumor activity and safety of BGB324, an Axl kinase inhibitor, when given in combination with pembrolizumab, the humanized monoclonal antibody (mAb) which targets the programmed death receptor-1 (PD-1) protein in patients with advanced or metastatic triple negative breast cancer (TNBC) or triple negative Inflammatory Breast Cancer (TN-IBC).

1.1 Triple Negative Breast Cancer and Inflammatory Breast Cancer

TNBC is a disease of exclusion describing any breast cancer that does not express estrogen or progesterone receptors or overexpress Her2. In total TNBC represents 15 to 25% of cases of breast cancer. As such the term represents a heterogeneous population although most cases in younger women are "basal – like" defined by the presence of cytokeratin 5/6 and epithelial growth factor expression on histology[4]. TNBC is more common in younger women, Africans, Hispanics and women with germline mutations of BRCA 1. Following initial therapy patients with TNBC have a much higher risk of recurrence during the first 3–5 years but this risk of recurrence drops sharply thereafter. The pattern of disease spread within the body is also different from other types of breast cancer with a much higher rate of intracerebral metastases. Current treatment is currently limited to cytotoxic chemotherapy and radiotherapy. TNBC is particularly sensitive to taxanes and anthracyclines, and because of the high risk of early relapse, patients often receive a combination of these drugs in the (neo)adjuvant setting. This limits the utility of the same drugs in the metastatic setting when many tumors have already become resistant. Although initial response rates to non- or partially cross resistant chemotherapy regimens are high chemosensitivity correlates poorly with overall survival and median survival for patients from the appearance of metastatic disease is 13 months[5]. As such there remains a significant unmet medical need for new approaches to the treatment of metastatic disease especially therapies that do not exhibit cross-resistance to existing cytotoxics.

Inflammatory breast cancer is a rare and very aggressive disease in which cancer cells block lymph vessels in the skin of the breast. Inflammatory breast cancer accounts for 1 to 5% of all breast cancers in the USA[6]. Most are invasive ductal carcinomas[7]. The disease progresses rapidly, and usually, at diagnosis, the disease is already stage III or IV. Like TNBC, inflammatory breast cancer is more common in younger women and women of African origin. It is also more often seen in obese women. Inflammatory breast cancers are often hormonal negative and therefore current treatment is limited to cytotoxic chemotherapy, surgery and radiotherapy. As with TNBC, taxanes and anthracyclines are the mainstay of the chemotherapy.

1.2 Rationale for Study BGBC007

There is a strong scientific/pre-clinical rationale for the use of BGB324 in TNBC and TN-IBC. There is no clinical data available from patients with these diseases.

BGB324 is a highly selective inhibitor of Axl kinase, a receptor tyrosine kinase enzyme associated with the epithelial-mesenchymal transition. TNBC reflects a heterogenous population of molecular subtypes. Typically, TNBC subtypes can be assigned to 3 intrinsic molecular subtypes: basal like, mesenchymal like and luminal like[8]. In TN-IBC, high tumoral expression of TIG1, a functionally undefined membrane protein confers shorter survival in patients with IBC. Axl kinase is a TIG1 binding protein – which regulates invasion of IBC cells by supporting the

Axl signaling pathway in IBC cells. TIG1 and Axl are highly expressed in patients with TNBC and IBC in particular[9].

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, **triple negative breast cancer** and Hodgkin's Lymphoma as determined by response rate (KEYNOTE-012). Keynote-012 was a multicenter, non-randomised phase 1b trial of single agent pembrolizumab given intravenously at 10 mg/kg every 2 weeks to patients with advanced PD-L1 positive (expression in stroma or ≥1% of tumor cells by IHC) TNBC, gastric cancer, urothelial cancer and head and neck cancer. Thirty-two women with TNBC were enrolled, of which, 27 were evaluable for anti-tumor activity and the overall response rate was 18.5%[10]. Further ongoing clinical trials in TNBC are being conducted - including a phase II clinical trial (KEYNOTE-86) and a phase III clinical trial (KEYNOTE-119). Ongoing clinical trials are also ongoing in other tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the pembrolizumab Investigator's Brochure.

The rationale to assess the safety and anti-tumor effect of BGB324 and pembrolizumab when given in combination, is based on the following:

- Dysregulation of the AXL receptor tyrosine kinase (RTK) enzyme has been associated with many types of cancer. AXL is one of 58 RTKs, and belongs to the TAM (tyro3, AXL, MER) subfamily. High levels of AXL expression have been associated with:
    - Poor prognosis in different cancers such as glioblastoma multiforma[11], breast (including inflammatory breast cancer)[9] and lung cancer[12], osteosarcoma[13], and acute myeloid leukemia[14];
    - Epithelial-mesenchymal transition (EMT)[15];
    - Developed drug resistance to targeted therapies[16,17,18] and chemotherapy[19,20].
    - EMT is the process consisting of multiple biochemical changes by which polarised epithelial cells gain a mesenchymal cell phenotype, leading to increased migration and invasive properties. In cancer, EMT is a hallmark of invading cells and consequently cancer/metastases.
    - BGB324 is a highly selective AXL kinase inhibitor.
- It is increasingly understood that cancers are recognized by the immune system and, under some circumstances, the immune system may control or even eliminate tumors[21]. However, if elimination is incomplete, the tumor may evolve mechanisms to avoid or attenuate the immune system. In the tumor microenvironment, PD-L1 expressed on tumor cells binds with PD-1 on activated T-cells reaching the tumor. This delivers an inhibitory signal to those T-cells, preventing them from killing the tumor cells, and thus, protecting the tumor from immune elimination[22]. Pembrolizumab is a PD-1 inhibitor (Section 1.6).
- A strong association between EMT status and an inflammatory tumor micro-environment with elevation of multiple targetable immune checkpoint molecules, including PD-L1, PD-1, PD-L2, BTLA, CTLA-4 etc. has been shown. Multiple agents, including

pembrolizumab, that target these checkpoint molecules, are in development for a range of cancers that are considered to have highly immunogenic microenvironments.

- Pre-clinically, BGB324 has been combined with PD-1 and PD-L1 inhibitors, and has been shown to potentiate the effect of PD-1/PD-L1 inhibition and to enhance tumor leukocyte infiltration in a TNBC orthotopic xenograft model and lung cancer syngeneic model in C57B1/6 mice (Section 1.3.1).
- There is therefore, a strong scientific rationale for combination of BGB324 with pembrolizumab in TNBC and IBC breast cancer. The proposed population will have advanced disease and therefore, the combination of BGB324 with pembrolizumab is expected to increase the response rate and prolong the duration of response.

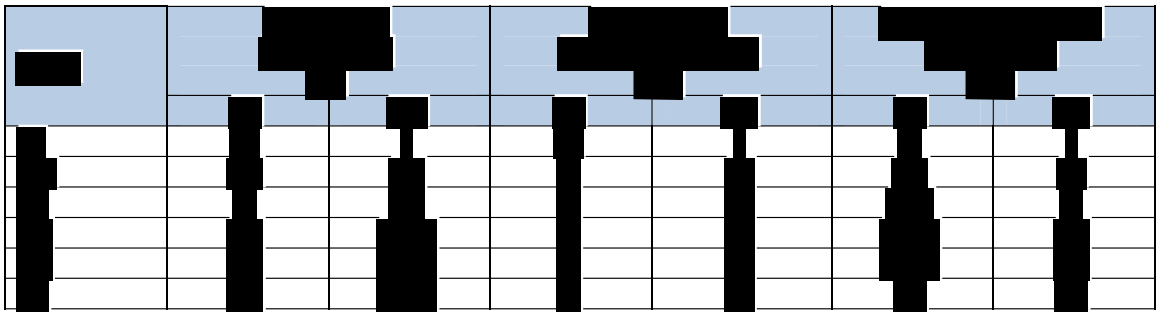
1.3 Non-Clinical Studies with BGB324

Please refer to the current version of the Investigator's Brochure for further details of the non-clinical studies with BGB324.

1.3.1 Non-clinical pharmacology of BGB324

BGB324 demonstrates potent inhibition of Axl in biochemical and cell-based kinase inhibition assays. The selectivity of BGB324 for Axl is illustrated in Table 6.

[redacted]



n/a = not applicable

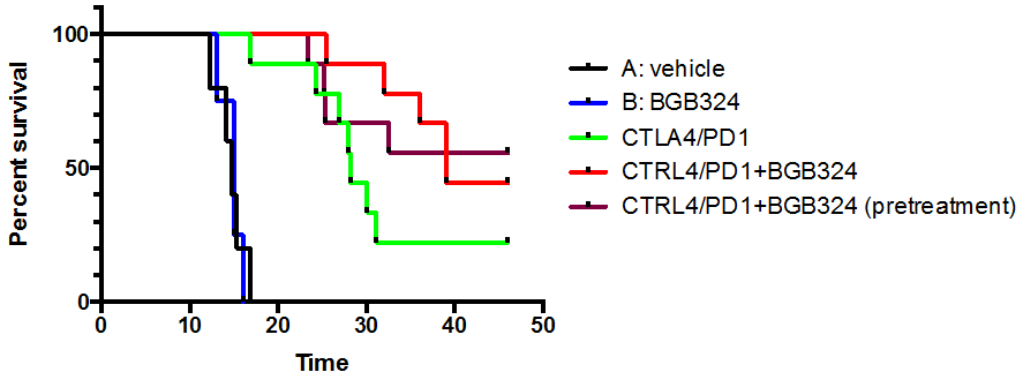
BGB324 inhibits the growth and survival of tumor cell lines derived from a range of solid and leukemic tumors.

The anti-tumor activity of BGB324 in combination with anti-mPD-1 and anti-mCTLA-4 was evaluated in a syngeneic 4T1 mammary adenocarcinoma model in Balb/c mice. In this poorly immunogenic 4T1–BalbC model, BGB324 potentiated the effect of anti-mCTLA-4 and anti-mCTLA-4+anti-mPD-1 antibodies and resulted in significantly increased median survival, more complete responders and reduced primary tumor growth. Responding mice were immune against re-challenge with 4T1 cells.

See the Investigator Brochure for details.

BGB324 in combination with PD-1 and CTLA-4 inhibitors potentially promotes survival in syngeneic mammary adenocarcinoma model (Figure 2):

Figure 2: BGB324 in combination with anti mCTLA4 and anti mPD-1



1.3.2 Non-clinical toxicology of BGB324

To support clinical studies with BGB324 a series of animal toxicology and safety studies, including 28-day repeat dosing studies in rodents and monkeys and a single dose telemetered cardiovascular (CV) safety study in monkeys, have been conducted. Comparisons of the data reported in the rodent and monkey studies indicate that primates are more sensitive to BGB324 on a per body weight basis.

The results of the repeat dose 28-day study in monkeys identified the liver, reticuloendothelial system and hematopoietic system as target organs. These events were largely thought to be due to macrophage accumulation, and were only partially reversible across the planned 16-day recovery period, although this was anticipated to be due to the slow elimination of the compound. Similar findings were identified in mice treated across a range of dose levels with partial recovery noted 16 days later.

In the CV safety study, single oral administration of BGB324 (7.5 mg/kg – 60 mg/kg) was associated with recoverable, non-adverse decreases in heart rate and corresponding increases in the RR interval durations. Dose-dependent increase in QTc interval was noted at all dose levels; the magnitude of the QTc effect at the highest dose level was 17%, whilst at 7.5 mg/kg and 15 mg/kg, the change generally fell below 10% compared to vehicle control and pre-dose values. These observations were consistent with the previously identified IC_{50} for human ether-à-go-go related gene (hERG) channel inhibition of 0.53 µM BGB324.

In an academic model of osteoporosis, BGB324 was administered in combination with high dose corticosteroids (12.5 mg/kg per day of prednisolone). In this research study, 6 out of 7 mice experienced severe toxicity after five continuous days of combination therapy. Four of the 6 animals (that developed severe toxicity) died and the other 2 were euthanized for humane reasons. The exact mechanism of this effect is currently under investigation. The mice received very high levels of corticosteroids to induce rapid onset of osteoporosis – on a mg/kg basis, the corticosteroid dose was 20 fold higher than a typical high dose commonly used in clinical practice. Additionally, the dose of BGB324 used in this model was 50mg/kg which is 6 fold higher than the maximum exposure observed in human clinical studies.

BGB324 was negative in the Ames bacterial mutation assay, suggesting that BGB324 is not mutagenic. BGB324 was also negative in an *in vitro* mammalian cell cytogenetic study in human lymphocytes suggesting that BGB324 is not clastogenic.

1.3.3 Pharmacokinetics and metabolism of BGB324

BGB324 had moderate to high plasma clearance (33.7, 18.7 and 43.3 mL/min/kg in rats, dogs and monkeys, respectively) i.e. plasma clearance approached hepatic blood flow in these species. Since BGB324 is sequestered into blood cells, blood clearance will be lower than plasma clearance at least in monkeys (monkeys are currently the only species tested). However, BGB324 was metabolically stable *in vitro* suggesting that liver metabolism was unlikely to contribute significantly to the elimination of BGB324 *in vivo*.

There was an inhibitory effect of BGB324 on cytochrome P450 (CYP) 3A4 IC50 1 to 5 micromolar; therefore, there is at least a moderate risk of interactions with co-administered drugs that are CYP3A4 substrates.

1.4 Clinical studies with BGB324

Please refer to the current version of the BGB324 Investigator's Brochure for further details of the clinical studies with BGB324.

A phase I, first-in-human study in healthy male subjects (Study BGBC001) has been completed.

Two phase 1b/2 clinical studies are currently underway in patients with advanced cancers: Study BGBC003 in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), and Study BGBC004 in patients with NSCLC. Study BGBC003 will define a recommended Phase 2 dose (RP2D) of single agent BGB324 in patients with advanced hematologic malignancy, then further evaluate the RP2D in an expansion phase. This expansion phase will also explore BGB324 given in combination with standard treatments for AML. Study BGBC004 will identify the RP2D for BGB324 given in combination with erlotinib in patients with NSCLC. The study will then continue to enroll to an expansion phase to further evaluate the effectiveness of BGB324 in combination with erlotinib.

1.4.1 Safety summary and reference safety information

The reference safety information below is based on a data cut of active trials on 31 March 2016 (8 April 2016 for serious adverse events (SAEs)) as presented in the IB V9.0 dated 28 July 2016. At the time of cut-off, 24 and 10 patients (including two who received BGB324 in combination with erlotinib) had received BGB324 in Studies BGBC003 and BGBC004, respectively. Please refer to the latest edition of the IB for the most up-to-date safety information during the conduct of this clinical study.

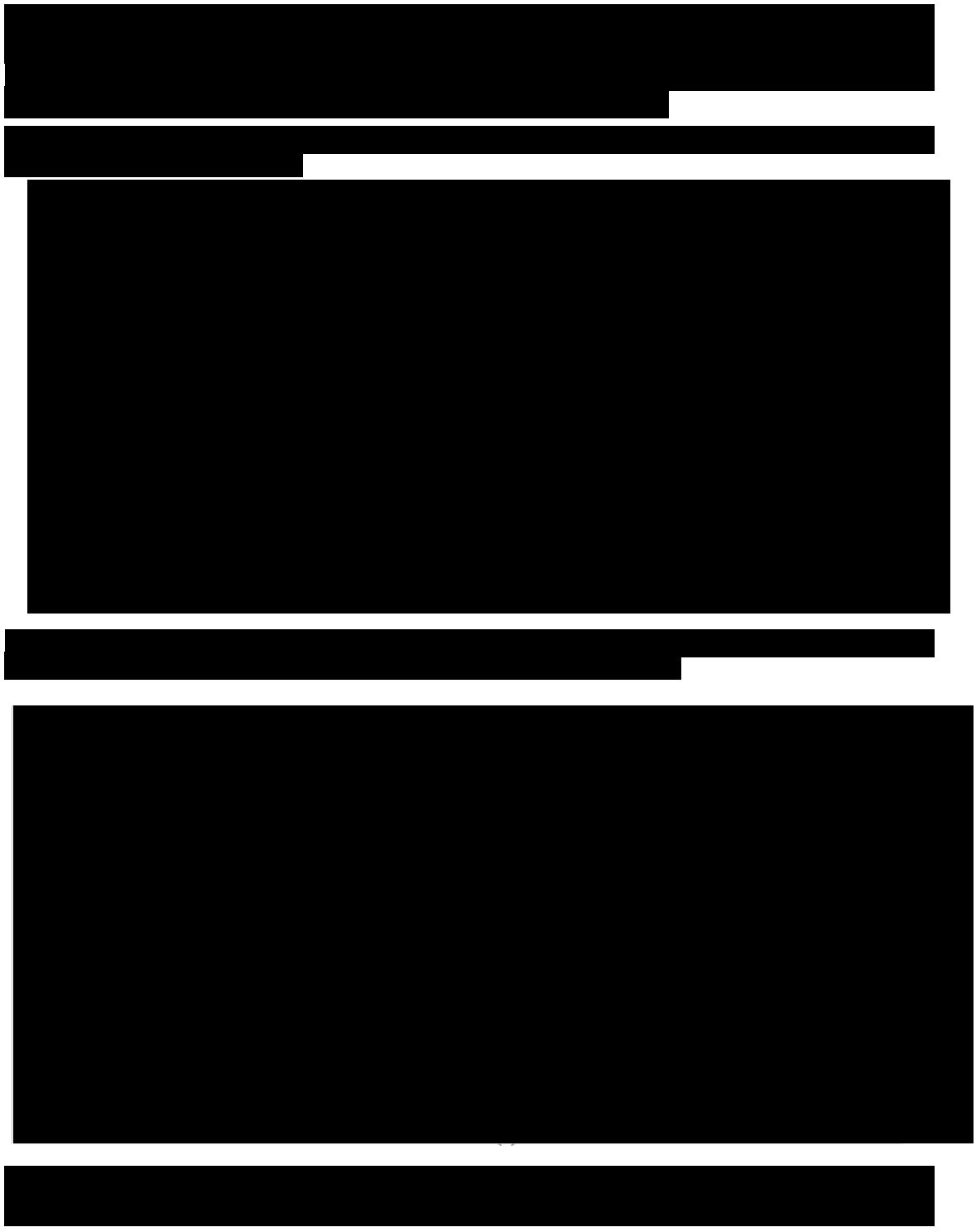
AEs to date assessed to be study treatment related following repeat oral doses of BGB324 in Studies BGBC003 and BGBC004 indicate that gastrointestinal disorders are the most commonly observed events (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 to 3) and were observed in approximately one half of patients treated in both repeat dose studies. In most cases these events responded well to symptomatic treatment and did not lead to treatment discontinuation or dose reduction. As expected the incidence of

infections was higher in the relapsed/refractory AML/MDS patient group whilst reversible increases in serum creatinine were more frequent in patients with NSCLC.

At the data cut-off date of 08 April 2016, valid SAEs had only been reported from patients treated in Study BGBC003. A total of 26 SAEs reports (with 36 events) in 16 patients have been recorded. The majority of SAEs are cardiovascular disorders and infections, including multiple cardiovascular disorders in one patient with MDS who had pre-existing ischemic heart disease who experienced two distinct episodes of myocardial infarction whilst receiving BGB324 which were considered unrelated to treatment with BGB324. The majority of the remaining reports are due to episodes of sepsis most commonly pneumonia which are common events in patients with myeloid malignancies. Three SAEs in two patients were study treatment-related. One 85-year old male patient with AML had an SAE of Grade 3 diarrhea, which was considered definitely related to study treatment. The intensity decreased to Grade 1 in response to adequate anti-diarrheal treatment. A 68-year old male patient with AML had two SAEs of myocardial ischemia and increased Troponin T which were considered probably related to study treatment. These events were recovering/resolving eight days later at the time of the patient's death from Grade 3 sepsis and upper gastrointestinal hemorrhage which were considered to be unrelated to treatment with BGB324.

To date there is limited clinical experience with BGB324, and therefore all related SAEs should be considered unexpected and require expedited reporting to the regulatory authorities as SUSARs (see current IB, together with any relevant addendum for further details).

[redacted]



[redacted]

1.6 Pembrolizumab Background and Clinical Trials

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

1.6.1 Rationale for pembrolizumab dose selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg, administered every 3 weeks (Q3W). The dose recently approved in the US and several other countries for treatment of melanoma and NSCLC subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, an open-label Phase I study conducted to evaluate the safety, tolerability, PK and pharmacodynamics (PD), and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the

200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab for the treatment of patients with TNBC and TN-IBC.

2 STUDY OBJECTIVES AND ENDPOINTS

The objective of this study is to assess the anti-tumor activity of the combination treatment of BGB324 and pembrolizumab in patients with previously treated locally advanced and un-resectable or metastatic triple negative breast cancer (TNBC) or inflammatory breast cancer (IBC). Table 9 presents the study objectives.

Table 9: Study Objectives and Endpoint (assessment)

Objective	Endpoint (Assessment)
Primary: • To assess anti-tumor activity of the combination of BGB324 and pembrolizumab	• Objective response rate (complete response and partial response)
Secondary: • To assess the safety of BGB324 and pembrolizumab when given in combination • To further assess the anti-tumor activity of the combination of BGB324 and pembrolizumab • To evaluate the pharmacokinetic profile of BGB324 when given with pembrolizumab.	• The number and frequency of adverse events; assessment of safety laboratory parameters, vital signs and ECGs • To include Disease Control Rate, Duration of Response; Progression-free Survival; 12-month Overall Survival • Assessment of pharmacokinetic variables including C_{max}, AUC, $t_{½}$
Exploratory: • To assess relevant biomarkers	• To assess PD-L1 and Axl expression in patients with TNBC and TN-IBC • To assess any correlation or association between expression level of PD-L1 and Axl and anti-tumor outcomes such as ORR • Assessment of relevant biomarkers in tumor and blood which support immune modulation and Axl signaling

3 SELECTION CRITERIA

The study will enroll adult patients with pre-treated, advanced or metastatic TNBC.

3.1 Inclusion Criteria

A patient will be suitable to proceed to treatment on study if they meet all of the following criteria:

1. Provision of signed informed consent.
2. Male and non-pregnant females who are aged 18 years or older at the time of provision of informed consent.
3. Histopathologically or cytologically documented TNBC or TN-IBC. Tumors must have been confirmed negative for ER and PR by IHC (<1% positive tumor nuclei, as per ASCO-CAP guideline recommendations[3]) and negative for HER2 by IHC or fluorescent or chromogenic in situ hybridization (FISH or CISH). Patients with equivocal HER2 results by IHC should have their negativity status confirmed by FISH.
4. Locally advanced and unresectable or metastatic TNBC or triple negative inflammatory breast cancer.
5. Received one or more prior therapies for TNBC or inflammatory breast cancer in the metastatic setting, and prior treatment (metastatic or (neo) adjuvant) must have included a prior taxane and/or anthracycline-based therapy
6. Has measurable disease as defined by RECIST 1.1[2] on computed tomography (CT) or magnetic resonance imaging (MRI) and as determined by the site study team. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Provision of suitable tumor tissue for the analysis of Axl kinase expression and PD-L1 expression. Suitable tumor tissue must consist of a minimum of newly acquired (fresh) tumor tissue sample (as a FFPE block), together with either further newly acquired tumor tissue (i.e. further FFPE block) or an archival tumor tissue sample (as a further FFPE block or further 10 unstained slides). See Section 5.3.13 for an explanation.
8. Eastern Cooperative Oncology Group (ECOG) performance score 0 or 1 (Appendix A).
9. Life expectancy of at least 3 months.
10. Adequate organ function confirmed at Screening and within 10 days of initiating treatment, as evidenced by:
    a. Platelet count ≥100,000 /mm^3;
    b. Hemoglobin ≥9.0 g/dL (≥5.6 mmol/L);
    c. Absolute neutrophil count (ANC) >1,500 /mm^3;
    d. Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN), or ≤5 times the ULN for patients with liver metastases;
    e. Total bilirubin ≤1.5 times the ULN, or direct bilirubin ≤ULN for patients with total bilirubin levels >1.5xULN.
    f. Creatinine ≤1.5 times the ULN or calculated creatinine clearance >60 mL/min

(by Cockcroft Gault formula; see Appendix B)

g. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 times the ULN and Activated Partial Thromboplastin Time (aPTT) ≤1.5 times the ULN. *Note: If patient is receiving anticoagulant therapy, then PT or PTT must be within therapeutic range of intended use of anticoagulants;*

h. LDH ≤2.5 times the ULN

11. Female patients of childbearing potential must have a negative pregnancy test (either urine or serum pregnancy test) within 3 days prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the patient received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
13. Patients of reproductive potential must be willing to practice highly effective methods of contraception (such as those described in Section 6.14) throughout the study and for 120 days after the last dose of study medication. Abstinence is acceptable if this is the usual lifestyle of the patient. Female patients are considered NOT of childbearing potential if they have a history of surgical sterility or evidence of post-menopausal status defined as any of the following:
    a. ≥45 years of age and has not had menses for more than 1 year;
    b. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle stimulating hormone (FSH) value in the postmenopausal range upon Screening evaluation and oestradiol <30pg/mL.
    c. Post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.

3.2 Exclusion Criteria

A patient will not be suitable to proceed to treatment on study if they meet any of the following criteria:

1. Has disease that is suitable for local therapy administered with curative intent.
2. More than 3 previous lines of therapy in the metastatic setting.
3. Has received prior therapy with an immunomodulatory agent.
4. Has a known additional malignancy that is progressing or requires active treatment. *Note: Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.*
5. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. *Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks prior to the first dose of trial treatment and any neurological symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.*

6. History of the following cardiac conditions:
   a. Congestive cardiac failure of >Grade II severity according to the NYHA (Appendix C: defined as symptomatic at less than ordinary levels of activity).
   b. Ischemic cardiac event including myocardial infarction within 3 months prior to first dose.
   c. Uncontrolled cardiac disease, including unstable angina, uncontrolled hypertension (i.e. sustained systolic BP >160 mmHg or diastolic BP >90 mmHg), or need to change medication due to lack of disease control within 6 weeks prior to the provision of consent.
   d. History or presence of sustained bradycardia (≤55 BPM), left bundle branch block, cardiac pacemaker or ventricular arrhythmia. *Note: Patients with a supraventricular arrhythmia requiring medical treatment, but with a normal ventricular rate are eligible.*
   e. Family history of long QTc syndrome; personal history of long QTc syndrome or previous drug-induced QTc prolongation of at least Grade 3 (QTc >500ms).
7. Abnormal left ventricular ejection fraction on echocardiography or MUGA (less than the lower limit of normal for a patient of that age at the treating institution or <45%, whichever is lower).
8. Current treatment with any agent known to cause Torsade de Points which cannot be discontinued at least five half-lifes or two weeks prior to the first dose of study treatment.
9. Screening 12-lead ECG with a measurable QTc interval according to Fridericia's correction >450 ms.
10. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study treatment.
11. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent. *Note: Subjects with ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.*
12. Received an anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of study treatment or who has not recovered (i.e. ≤Grade 1 or baseline) from AEs due to agents administered more than 4 weeks earlier.
13. Major surgery within 28 days prior to start of study treatment and failure to have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study treatment. *Note: Major surgery does not include procedures for insertion of venous catheters or biopsies*.
14. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoetin) within 4 weeks prior to the first dose of study treatment. *Note: Patients receiving stable dose of growth factors with a hemoglobin value that meets Inclusion Criterion 10b may be included.*

15. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
16. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). *Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment*.
17. Known history of human immunodeficiency virus (HIV 1/2 antibodies).
18. Has known active infection with Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). *Note: i) Patients with a history of hepatitis B infection are eligible provided they are hepatitis B surface antigen negative ii) Patients with a history of hepatitis C infection are eligible provided they have no evidence of hepatitis C RNA using a qPCR at least 6 months after completing treatment for hepatitis C infection.*
19. Has received a live-virus vaccination within 30 days of planned treatment start. *Note: Seasonal flu vaccines that do not contain live virus are permitted.*
20. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis
21. Has a history of interstitial lung disease.
22. Inability to swallow or tolerate oral medication.
23. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohn's disease, or previous bowel resection which is considered to be clinically significant or could interfere with absorption.
24. Known lactose intolerance.
25. Requires vitamin K antagonists. *Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included. Note: Factor Xa antagonists are permitted.*
26. Treatment with any of the following: histamine receptor 2 inhibitors, proton pump inhibitors or antacids within 7 days of start of study treatment.
27. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index.
28. Known severe (≥Grade 3) hypersensitivity to BGB324, pembrolizumab, and/or any of their excipients.
29. Has an active infection requiring systemic therapy (apart from cutaneous infections).
30. Has a history or current evidence of any condition, therapy, or laboratory abnormality that, in the opinion of the Investigator, might confound the results of the trial, interfere with the patient's participation and compliance in the trial, or means it is not in the best interests of the patient to participate.
31. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting from Screening through to 120 days after the last dose of study treatment.
32. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.3 Patient Withdrawal of Consent and Discontinuation of Treatment

Patients may withdraw their consent to further treatment on study or withdraw their consent to any further participation in any further assessments at any time without stating a reason and without prejudice to further treatment.

Patients who have withdrawn their consent to receive further treatment, but not withdrawn their consent to further participation in the study, are expected to continue in follow-up to enable assessment of the duration of their response and other endpoints until confirmed progression and then survival status.

Patients who discontinue BGB324 treatment (for reasons other than disease progression) may be able to continue with (monotherapy) pembrolizumab until 106 weeks (that is, 35 completed cycles of pembrolizumab, equivalent to 24 calendar months).

Patients who discontinue pembrolizumab (for reasons other than disease progression) may be able to continue with BGB324 for up to 106 weeks (equivalent of 24 calendar months).

A Post Treatment Visit should be performed 30 +/-3 days after the last dose of study treatment (BGB324 and/or pembrolizumab), to enable follow up safety assessments and further tumor assessment where required.

The Investigator may discontinue study treatment at any time. Example reasons for discontinuing study treatment are:

- Patient withdrawal of consent to further treatment and/or further participation in the study.
- Disease progression (note that treatment can continue if progression is suspected in the absence of clinical deterioration – progression is to be confirmed no less than 4 weeks after the initial observation).
- The patient experiences a toxicity, considered related to BGB324, including those necessitating a BGB324 dose delay of >14 days (Section 6.6), and where the re-introduction of BGB324 (including a dose reduction of BGB324), is not considered suitable.
- The patient experiences a toxicity, considered to be related to treatment with pembrolizumab which necessitates pembrolizumab treatment withdrawal (Section 6.6.3).
- Other toxicities or events, unrelated to BGB324 or pembrolizumab, that would, in the Investigator's opinion, prevent the patient from continuing on study treatment(s).
- Treatment non-compliance. (All documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance of study visits must be followed-up by the Investigator to obtain the reason for where possible. For further information on treatment non-compliance, please see also Section 3.5).
- Pregnancy.

A patient is defined as 'lost to follow-up' only if every effort has been made to contact the patient and determine the patient's willingness to continue with all or some of the study assessments (irrespective of whether the patient is still receiving study treatment).

Patients who are unwilling to continue to receive further treatment are expected to continue in follow-up to enable assessment of the duration of their response and other endpoints until confirmed progression and then survival status.

The Sponsor reserves the right to request the withdrawal of study treatment from a patient due to protocol violation or other significant reason.

3.4 Permitted Cessation of Pembrolizumab Treatment on Study

Note that Investigators may wish to stop pembrolizumab treatment per local treatment practice for patients who have attained a confirmed complete response (CR) that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Patients will remain on study and continue to receive BGB324 treatment and continue disease assessments.

Once pembrolizumab treatment has been stopped for this reason, it cannot be restarted on study.

3.5 Definition of Evaluable Patient, Acceptable Treatment Compliance and Replacement of Patients

Patients will be replaced if they are considered to be non-evaluable. An evaluable patient is one that has received at least one combination dose and has measureable disease according to the Investigator site assessment.

Patients who have failed screening (usually because they have failed one or more of the inclusion or exclusion criteria) will not receive study treatments and are considered not to be evaluable.

Treatment non-compliance for this study will be defined as follows:

- For BGB324: missing more than 7 doses in any 21-day period (other than a dose delay for toxicity management (see Section 6.6.1 and Section 6.6.2) or an interruption for corticosteroid administration (Section 6.8)).
- For pembrolizumab: Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (for example, elective surgery, unrelated medical events, patient vacation etc). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for the interruption should be documented in the patient's study notes.

3.6 Procedures for Patient Cessation of Study Treatment

When a patient stops or discontinues one or both of their study treatments, the reason for cessation will be recorded in the patient file and the Case Report Form (CRF). Patients must complete a post treatment visit, and continue with their scans and assessments of disease (if the patient has not already progressed) and/or survival status.

3.7 Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority officials discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.
- Failure of the Investigator(s) to comply with pertinent clinical trial regulations.
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or Competent Authority.
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in accordance with applicable local regulations.

4 STUDY DESIGN

This is an open-label, multi-center, single arm, phase II study to assess the anti-tumor activity and safety of BGB324 in combination with pembrolizumab in patients with previously treated locally advanced and unresectable disease or metastatic TNBC or TN-IBC.

The study will utilize a 2-stage, single arm, extension of Simon's 2-stage design[1] with one interim and a final analysis. The interim analysis will be conducted when 28 patients are evaluable for ORR. If 5 or fewer responses are observed in up to 28 patients, the trial will be terminated in favor of the null for futility. If 11 or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Where 6 to 10 patients have an observed response at the interim analysis, up to a further 28 patients may be evaluated, for a total of 56 patients (see Section 8.1), taking the overall risk: benefit of the combination into consideration.

BGB324 will be administered orally once daily. On the first 3 days of administration, the BGB324 dose will be a 'loading' dose of 400 mg on Days 1, 2 and 3. From Day 4 onwards, patients will receive a daily dose of 200 mg. A fixed dose of 200 mg pembrolizumab will be given by intravenous (i.v.) infusion over 30 minutes every 3 weeks in all patients. The 3-weekly pembrolizumab dosing schedule will be used to define 3-week treatment cycles throughout the treatment period of the study.

The BGB324 and pembrolizumab dose levels selected for this study are summarized in Table 10.

Table 10: BGB324 and pembrolizumab dosing

BGB324:	**Loading Dose: Days 1, 2 & 3**	**Daily Dose: Day 4 onwards**	**Frequency**	**Route of administration**
Dose level	400 mg	200 mg	Daily	Oral
Dose level -1	200 mg	100 mg	Daily	Oral
Pembrolizumab	**Dose**	**Regimen**	**Frequency**	**Route of administration**
	200 mg	Day 1 of each cycle	Every 3 weeks	i.v.

Dosing of both drugs will commence on Day 1. On days when both BGB324 and pembrolizumab are given, pembrolizumab will be given first and patients will be observed for 1 hour for infusion and other AEs. BGB324 may then be administered.

4.1 Safety Run-In

Pembrolizumab has not previously been combined with BGB324 in patients (in any indication) and therefore, a safety run-in will include a total of 12 patients. The internal DRC will conduct a review of the safety data from the first 6 patients who have had the potential to be followed for at least 6 weeks (min 2 cycles), and then again after a further 6 patients (12 patients in total) have

had the potential to be followed for at least 6 weeks. At each of these safety reviews, the DRC will consider the rate of BGB324 dose reductions and the rate of permanent discontinuation from BGB324 and pembrolizumab.

The DRC will consider whether to recommend a lower dose of BGB324 (dose level -1) for new patients. Dose level -1 is defined as 200 mg BGB324 on Days 1, 2 and 3, followed by 100 mg from day 4 onwards.

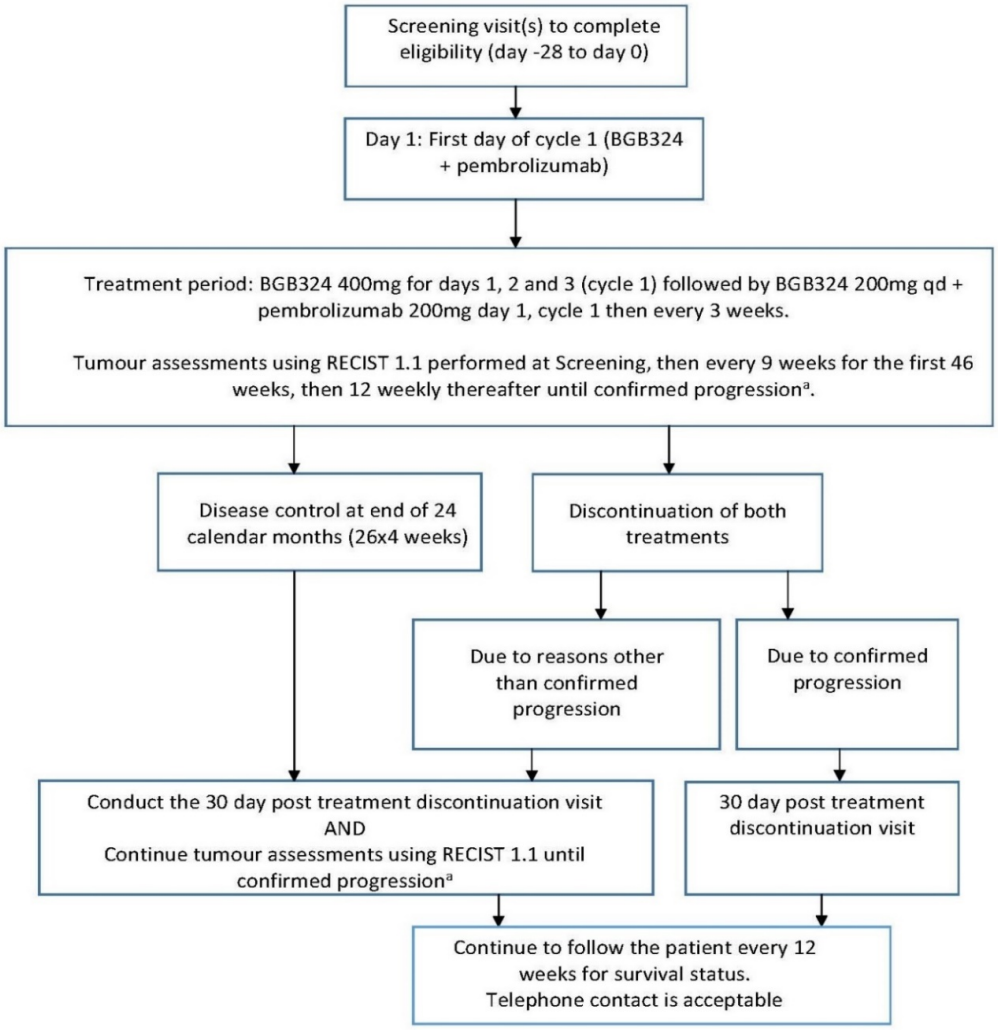
For the safety run-in reviews, each patient will have had the potential to receive (as a minimum):

- 2 cycles of pembrolizumab;
- BGB324 at 400 mg for 3 days, followed by 200 mg daily for ~ 6 weeks.

The DRC, consisting of Principal Investigators, the Sponsors' (BerGenBio and Merck) Medical Monitors, and invited experts as required, will review all patient safety data, including SAEs, AEs, laboratory and ECG results, dosing information, including dose reductions and permanent discontinuations.

Where there is a suggestion of an immune response leading to a false categorization of disease progression, results from later tumor imaging time points may be used for the objective response assessment following the 2-stage single arm design. The Sponsor may request ad-hoc DRC meetings at any time during the study to assess interim safety data and review the need for dose modifications. For more details on the dose modification rules for BGB324 and pembrolizumab, please refer to Section 6.6.

Figure 5: Flow Chart



[a]Progression needs to be confirmed at the next scheduled visit and no earlier than 4 weeks in the absence of clinical deterioration. Treatment can continue until confirmed progression.

4.2 Duration of Treatment

BGB324 and pembrolizumab will be given until disease progression (in the absence of clinical deterioration, treatment can continue and disease progression should be confirmed after 4 weeks) or until an unacceptable toxicity has occurred which necessitates treatment withdrawal (Section 6.6), or until 106 weeks (35 cycles), equivalent to 24 calendar months. Patients participating in clinical trials with pembrolizumab receive treatment for a maximum duration of 2 years (35 cycles of therapy). This is consistent across the whole pembrolizumab development program.

Responses to pembrolizumab are expected to be durable, and the duration of response after stopping pembrolizumab continues to be evaluated and monitored across the pembrolizumab program.

Patients who discontinue BGB324 treatment (for reasons other than disease progression) may be able to continue with (monotherapy) pembrolizumab until 106 weeks (that is, 35 completed cycles of pembrolizumab, equivalent to 24 calendar months).

Patients who discontinue pembrolizumab (for reasons other than disease progression) may be able to continue with BGB324 for up to 106 weeks (equivalent of 24 calendar months). Otherwise, in the absence of progression, toxicity, or other reason for stopping treatment, pembrolizumab in combination with BGB324 will be given until the end of cycle 35 (this cycle ends at approximately week 106, 24 months).

5 STUDY SCHEDULE

The study consists of a Screening period, Treatment period, Post Treatment Visit and Follow-up period. Patients will attend the clinic for Screening period assessments up to 28 days before receiving the first dose of study treatment. The Post Treatment Visit will occur 30 days after the patient has discontinued both study treatments. All patients will continue in follow-up visits and continue to have their disease assessed and scanned (unless progression of disease has already been confirmed) and for survival status.

The study schedule will continue in keeping with the Study Assessment calendar. Patients will be required to visit the study sites for each study visit (which includes each pembrolizumab dose). From Cycle 2 onwards, a tolerance window of +/- 3 days is permitted. Pembrolizumab that cannot be given within these tolerance windows will be treated as a missed dose, although it is acceptable to have a pembrolizumab dose interruption for up to 3 weeks (for reasons other than toxicity). See Section 6.6.3 for full details on pembrolizumab dose interruptions, including the duration of interruption for toxicity.

It is important that the calendar schedule for tumor assessment relative to Cycle 1, Day 1 is maintained (subject to permitted tolerance windows). If treatment administration is misaligned with weeks (e.g. because of treatment delay), the tumor assessment schedule should be maintained by week number (**Table 3**, **Table 4** and **Table 5**). The schedule of disease assessment is every 12 weeks once a patient has stopped one or both or completed their (combination) treatment in the absence of progression.

Assessments requiring specific timing relative to the BGB324 or pembrolizumab dose are described in the footnotes to Schedule of Study Assessment **Table 4** and **Table 5**.

5.1 Schedule of Study Assessments

This section provides a list of study assessments described by visit. All procedures and assessments should be conducted pre-dose unless otherwise specified. A summary of this information is also provided in the Schedule of Study Assessment **Table 4** and **Table 5** and the associated footnotes. Additional assessments may be conducted as clinically indicated.

5.1.1 Schedule of Study Assessment – Year 1 and Year 2

Screening (up to 28 days prior to Day 1)

- Demographics – gender, ethnicity, race, age (birth month and year)
- Medical history
- Inclusion/exclusion checks
- Pregnancy or FSH and oestradiol levels (as appropriate)
- ECOG PS
- Vital signs
- Physical examination
- Clinical chemistry
- Hematology
- Coagulation
- Urinalysis

- ~ Thyroid function tests
- ~ Echocardiogram (or MUGA)
- ~ ECG (triplicate tests)
- ~ Tumor imaging
- ~ Disease Assessment
- ~ Tumor biopsy (fresh tissue mandatory; archival optional)
- ~ Biomarkers
- ~ Concomitant medication

Cycle 1, Day 1 (21 day cycle)

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Urinalysis
- ~ ECG (triplicate tests; pre-dose and at 6 hours post dose)
- ~ Biomarkers (if not collected at Screening)
- ~ Pembrolizumab 200 mg fixed dose - infusion
- ~ BGB324 oral dosing 400 mg
- ~ PK sampling - BGB324 pre-dose, 2, 4, 6 and 8 hours post dose
- ~ PK sampling for storage - pembrolizumab (pre-dose)
- ~ Adverse events
- ~ Concomitant medication

Cycle 1, Day 2

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ ECG (triplicate test; pre-dose)
- ~ BGB324 oral dosing 400 mg
- ~ PK sampling - BGB324 (pre-dose)
- ~ PK sampling for storage - pembrolizumab (pre-dose)
- ~ Adverse events
- ~ Concomitant medication

Cycle 1, Day 3

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology

- ~ ECG (triplicate test pre-dose)
- ~ BGB324 oral dosing 400 mg
- ~ PK sampling - BGB324 pre-dose, 2, 4, 6, 8 hours post dose.
- ~ PK sampling for storage – pembrolizumab (pre-dose)
- ~ Adverse events
- ~ Concomitant medication

Cycle 1, Day 4

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ ECG (triplicate test; pre-dose)
- ~ Biomarkers
- ~ BGB324 oral dosing 200 mg (consecutive daily dosing 21 day cycle)
- ~ PK sampling - BGB324 (pre-dose)
- ~ PK sampling for storage – pembrolizumab (pre-dose)
- ~ Adverse events
- ~ Concomitant medication

Cycle 1, Day 8

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Urinalysis
- ~ ECG (triplicate test; pre-dose)
- ~ Biomarkers
- ~ BGB324 oral dosing 200 mg (consecutive daily dosing 21 day cycle)
- ~ PK sampling - BGB324 (pre dose)
- ~ PK sampling for storage (pre-dose) - pembrolizumab
- ~ Adverse events
- ~ Concomitant medication

Cycle 1, Day 15

- ~ Vital signs
- ~ Physical examination
- ~ Clinical chemistry
- ~ Hematology
- ~ Coagulation
- ~ Urinalysis

- ECG (triplicate test; pre-dose)
- BGB324 oral dosing 200 mg (consecutive daily dosing 21 day cycle)
- PK sampling BGB324 (pre-dose)
- PK sampling for storage (pre-dose) - pembrolizumab
- Adverse events
- Concomitant medication

Cycle 2-35 (every 3 weeks), Day 1

- ECOG PS
- Vital signs
- Physical examination
- Clinical chemistry
- Hematology
- Coagulation
- Urinalysis (performed on Cycle 2 Day 1 only)
- Pregnancy test (if applicable)
- Thyroid function tests (performed at Cycles 3, 5, 7, 9, 11, 13, 15, 17 only in Year 1 and then Cycles 19, 21, 23, 25, 27, 29, 31, 33, 35 in Year 2)
- Echocardiogram (or MUGA) (performed at Cycles 9 and 17 in Year 1 and then Cycles 25 and 33 in Year 2)
- ECG (triplicate test; pre-dose)
- Tumor imaging (performed at Cycles 4, 7, 10, 13, 16, 20, 24, 28, 32 or Weeks 10, 19, 28, 37, 46, 58, 70, 82, 94, 106, and then every 12 weeks until progression)
- Disease assessment (performed at Cycles 4, 7, 10, 13, 16, 20, 24, 28, 32 or Weeks 10, 19, 28, 37, 46, 58, 70, 82, 94, 106, and then every 12 weeks until progression)
- Tumor biopsy (up to 2 optional post treatment biopsies)
- Biomarkers (performed only at Cycles 2-9)
- Pembrolizumab 200 mg fixed dose (infusion)
- BGB324 dosing 200 mg (daily oral dosing 21 day cycle)
- PK sampling BGB324 (pre-dose Cycles 2 and 3 only)
- PK sampling - pembrolizumab (pre-dose Cycles 2 and 3 only)
- Adverse events
- Concomitant medication

Post Treatment Visit **(only after both treatments are discontinued in either Year 1 or Year 2)**
+30 days from last dose of study treatment(s)

- ECOG PS
- Vital signs
- Physical examination
- Clinical chemistry
- Hematology
- Coagulation

- ~ Urinalysis
- ~ Thyroid function tests
- ~ ECG (triplicate test)
- ~ Adverse events
- ~ Concomitant medication
- ~ Tumor imaging (where applicable – for example, to confirm progression)
- ~ Disease assessment (where applicable – for example, to confirm progression)
- ~ Tumor biopsy (optional) at progression

Follow-Up (if the patient has had a Post Treatment visit in Year 1 or Year 2) - every 12 weeks

- ~ Concomitant medication (where applicable)
- ~ Tumor imaging (where applicable; every 12 weeks until disease progression)
- ~ Disease assessment (where applicable; every 12 weeks until disease progression)
- ~ Subsequent anti-cancer treatment
- ~ Adverse events (where applicable, see Section 7.4 and Section 7.5)
- ~ Survival status – this can be done by telephone.

5.2 Volume of Blood Sampling

Total blood volumes required during study participation will be provided in Informed Consent form provided to each patient. The Laboratory Manual will also describe unit and total blood volumes and provide examples based on various durations on study. Efforts will be made to limit PK and PD blood-letting during the study where on-going data analysis during the study suggests redundancy in sampling. Any such reductions in requirements for PK and PD blood sampling will be described and maintained in the Laboratory Manual.

5.3 Description of Study Interventions and Assessments

Details of the procedures to be followed for specified study assessments are provided. Additional assessments may be carried out as clinically indicated.

5.3.1 Demography and medical history

There will be a baseline assessment of demography (gender, race, ethnicity age (birth month and year) and medical history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses in the CRF. Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation), that worsen in severity or frequency from the time of signing the consent form, but before treatment allocation need to be reported as an AE if the event causes the patient to be excluded from the trial or is a result of a protocol specific intervention (Section 7.1).

5.3.2 Pregnancy, FSH and oestradiol test

Female patients of reproductive potential will have a pregnancy test carried out at Screening. This test must be carried out within 3 days prior to first study drug administration. A urine test is acceptable; however, a positive or equivocal urine test must be confirmed by a blood test. Patients confirmed as pregnant will be excluded from participation in the clinical study.

Female patients of reproductive potential will continue to have a pregnancy test before each cycle of pembrolizumab, or monthly.

Female patients who require documented confirmation of post-menopausal status will have their FSH and oestradiol levels assessed at Screening. Where post-menopausal status is not confirmed, patients will be required to undergo pregnancy testing per protocol to confirm suitability to proceed to dosing.

5.3.3 ECOG performance score

ECOG performance score (PS) will be assessed at the times given in Schedule of Study Assessment **Table 4** and **Table 5**. Details of the ECOG PS categories are presented in Appendix A. Patients must be confirmed as ECOG PS 0 or 1 at Screening in order to be eligible for study participation.

5.3.4 Vital signs

Vital sign parameters will be taken at the times given in Schedule of Study Assessment **Table 4** and **Table 5**. The date and time of collection will be recorded in the source data and on the CRF.

Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure and respiratory rate.

If any clinically significant findings are identified during the assessment of vital signs, the Investigator will record it as part of the medical history prior to start of dosing and as an AE post dose, where the finding represents a change from baseline. Findings identified prior to start of dosing must be checked against the study exclusion criteria (Section 3.2).

5.3.5 Physical exam

A physical examination, including measurement of weight, will be taken at the times given in Schedule of Study Assessment **Table 4** and **Table 5**. The patient's height will be measured at Screening. The patient's weight will also be assessed at Screening and at the start of every cycle. Height and body weight will be obtained while the patient is wearing light clothing (without shoes).

A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the Screening assessment, the physical examination may be reduced to a symptom-directed assessment.

If any clinically significant findings are identified during the physical examination, the Investigator will record it as part of the medical history prior to start of dosing and as an AE post dose, where the finding represents a change from baseline.

5.3.6 Clinical chemistry, hematology, coagulation and urinalysis

Blood and urine samples for determination of clinical chemistry, hematology, coagulation and urinalysis parameters will be taken at the times given in Schedule of Study Assessment **Table 4** and **Table 5** and prior to administration of study treatment. The date and time of collection will be recorded in the source data and on the CRF.

All testing will be performed at each site's local laboratory. Coagulation parameters may be assessed from the hematology sample.

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to the analysis of their first patient sample.

The laboratory variables to be measured are described in Appendix E.

If any clinically significant findings are identified from the safety lab assessments, the Investigator will record it as part of the medical history prior to start of dosing and as an AE post dose, where the finding represents a change from baseline. Findings identified prior to start of dosing must be checked against the study inclusion and exclusion criteria (Section 3.1 and Section 3.2).

5.3.7 Thyroid function test

Blood samples for thyroid function testing will be taken at the times given in Schedule of Study Assessment **Table 4** and **Table 5**. The date and time of collection will be recorded in the source data and on the CRF.

The thyroid assessment panel should include:

- Triiodothyronine (T3) or Free Triiodothyronine (FT3)
- Free thyroxine (FT4)
- Thyroid stimulating hormone (TSH)

All testing will be performed at each site's local laboratory. This assessment may be performed from the clinical chemistry sample (Section 5.3.6). Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to the analysis of their first patient sample. Laboratory variables to be measured are described in Appendix E.

If any clinically significant findings are identified, the Investigator will record it as part of the medical history prior to start of dosing and as an AE post dose, where the finding represents a change from baseline. Findings identified prior to start of dosing must be checked against the study inclusion criteria (Sections 3.1).

5.3.8 Echocardiography or MUGA

An echocardiography or MUGA assessment will be performed at Screening, and after every 6 months (every 8 cycles thereafter i.e. Cycle 9, Day 1, Cycle 17, Day 1, Cycle 25, Day 1, Cycle 33 Day 1).

Clinically significant findings identified prior to start of dosing must be checked against the study exclusion criteria (Section 3.2).

Patients who discontinue BGB324, but continue with monotherapy pembrolizumab, will stop undergoing an echocardiogram or MUGA assessment. Their final echocardiogram / MUGA assessment will occur if their next scheduled assessment is within the next 6 weeks (of discontinuing BGB324).

5.3.9 Electrocardiogram

A resting 12-lead ECG will be performed at the times given Schedule of Study Assessment **Table 4** and **Table 5**. Each assessment time point must be performed in triplicate.

All 12-lead ECGs should be recorded while the patient is in the supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual patients. The Investigator or designated physician will review the ECG results.

If any clinically significant findings are observed on the ECG, the Investigator will record it as part of the medical history prior to the start of dosing, and as an AE post dose where the finding represents a change from baseline. Clinically significant findings identified prior to start of dosing must be checked against the study exclusion criteria (Section 3.2). Note that the average value of the three assessments performed at each time point should be applied, except at Screening, where both the Screening and pre-dose Cycle 1 Day 1 assessments should be combined. Patients may be excluded based on the initial triplicate assessment at Screening.

Patients who discontinue BGB324, but continue with monotherapy pembrolizumab will stop undergoing an ECG.

Patients who have a BGB324 interruption of 14 days for toxicity (see Table 12 and Table 13) will require an ECG twice weekly for the 2 weeks following recommencement of BGB324 daily dosing. This is to ensure cardiac safety monitoring whilst BGB324 returns to steady state.

5.3.10 Tumor imaging

Efficacy endpoints in this study, including ORR, DoR, PFS will all be based on tumor imaging evaluation by RECIST 1.1[2].

RECIST assessments will be performed at the times given in Schedule of Study Assessment Table 4 and Table 5 using contrast-enhanced CT (preferred method) or MRI assessments of chest, abdomen, and pelvis. X-ray scans can be used where appropriate. Bone scans and brain scans should be conducted in the 6 weeks prior to study entry. Subsequently, x-ray, bone scans and brain scans will be used as appropriate. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up.

Baseline assessments should be performed no more than 28 days before start of study treatment (6 weeks for brain and bone scans), and ideally should be performed as close as possible to the start of study treatment. The Screening imaging assessments must confirm the patient has measurable disease per RECIST 1.1[2] (see Section 3.1).

For each patient, the same modality used at Screening must be used serially throughout the duration of study participation. All imaging procedures will be performed according to standard local imaging protocols to ensure consistency across study assessments.

All radiological and non-radiological (e.g. MRI) scans will be reviewed by the local site investigator; and if possible, stored electronically (de-identified with the patient's notes) at site.

A maximum of 5 target lesions (TLs) must be selected at baseline. All target lesions are measurable. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. All remaining lesions present at baseline are considered non-target, irrespective of whether they are measurable.

Disease assessments will be performed as per the schedule described in Table 3, Table 4 and Table 5 – that is, every 9 weeks ±7 days for the first 46 weeks relative to the date of first treatment administration and then every 12 weeks ±7 days thereafter until confirmed objective disease progression as defined by RECIST 1.1[2] (irrespective of a delay to treatment, or the reason for stopping treatment or subsequent therapy).

Any other sites at which new disease is suspected should also be adequately imaged at a follow-up visit.

If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

In addition to performing further scans where clinically indicated, scans also should be performed, as appropriate, to confirm response or disease progression.

5.3.11 Disease assessment

A disease assessment according to RECIST 1.1[2] will be performed and all measurements of existing target lesions and new or existing non target lesions will be recorded in the CRF whenever a tumor imaging assessment is made during the Treatment period, Post Treatment Visit or during Follow Up Visits.

For more information on data evaluation by RECIST 1.1[2] for studies with checkpoint inhibitors, please refer to Section 8.5.

5.3.12 Biomarkers

Evaluation of biomarkers will be performed at the time points described in Schedule of Study Assessment Table **4** and Table 5.

Blood samples will be collected at these time points to prepare PMBC and blood samples for assessment of Axl inhibition and other relevant markers including sAxl such as MAPK signaling pathway intermediates (ERK/pERK), pAxl expression and T-cell populations, Akt, pAkt, SLFN11, Bcl2, and Puma.

Patients who discontinue BGB324, but continue with pembrolizumab monotherapy are not required to provide further blood samples for biomarker evaluation.

Full details of the blood volumes required, plus requirements for sample collection, handling and shipment to the assigned central laboratory, will be described in Laboratory Manual for the study.

5.3.13 Tumor Sample Requirements

All patients are required to provide a fresh (newly acquired) tumor biopsy at Screening. Tumor specimens are to be submitted in sufficient quantity to allow for PD-L1 IHC and Axl IHC analysis (see the Pathology Manual).

Samples with limited tumor content (<100 viable tumor cells), cytology, cell block, decalcified or formalin fixed but previously frozen, frozen sample, plastic embedded, bone, bone marrow, clot and fine needle aspirates are inadequate for defining tumor PD-L1 and Axl status.

Axl expression can only be obtained from a fresh (newly acquired) tumor tissue sample. PD-L1 expression can be determined from either a fresh (newly acquired) or archival sample. In all cases, the tumor tissue must not have been previously irradiated.

Different testing laboratories will be used for Axl kinase and PD-L1 expression.

The fresh (newly acquired) tumor tissue sample will be either newly obtained core needle biopsy (minimum gauge 18) or newly obtained excisional biopsy.

The following tumor tissue options are available (all options require fresh tumor tissue sample, however, if there's insufficient fresh tumor tissue available, the 3rd option below allows the submission of archival tissue in addition to the fresh tissue sample):

- Where only a core needle biopsy is used, a minimum of 4 core biopsy samples are required. These should be placed in formalin and processed into 2 single paraffin embedded (FFPE) blocks (2 cores in one block and 2 cores in the other block) within 24-48 hours.
- Alternatively, where only a newly obtained excisional biopsy sample is used, this biopsy should be processed into 2 paraffin embedded (FFPE) blocks within 24-48 hours.
- Alternatively, 2 core needle (fresh tumor) biopsies or a single newly obtained excisional biopsy sample can be submitted (processed into one FFPE block), together with either an archival (FFPE) tumor tissue block or a minimum of 10 unstained slides each 5µm cut from the archival tumor sample block. The unstained slides must arrive at the testing laboratory within 14 days. In this option, an archival FFPE block is strongly preferred over unstained slides.

Archival blocks must be clearly labelled as archival.

Slides cut from an archival tissue block must be clearly marked as having come from an archival block.

Finally, where patients also have (additional) archived biopsy material which is suitable for additional (such as exploratory) biomarker assessment a sample of this material (either as an archival FFPE block or slides cut (and paraffin dipped) from the archival block) can also be prepared for study biomarker assessment. The patient will be offered a separate optional patient consent to enable this 'archival biomarker tumor sample' to be submitted.

Optional 'on study' tumor tissue (fresh tissue) biopsies can be conducted on up to 2 separate occasions on suitable lesions (for example, lesions that have progressed). Separate patient consent is required for these 'on study' biopsies.

Full details of the requirements for both fresh and archival biopsy sample collection, handling and shipment to the assigned (central) laboratories, will be described in the Pathology and Laboratory Manuals for the study.

5.3.14 Pharmacokinetics

Blood samples will be collected for the evaluation of the levels of BGB324 and pembrolizumab in plasma at the time points described in Schedule of Study Assessment Table 4 and Table 5.

Nominal PK blood sampling times should be adhered to as closely as possible. It is essential that the actual time and date of collection of each blood sample be recorded in the patient's records and in the CRF.

Full details of sample collection and handling for these samples will be described in Laboratory Manual for the study.

Full details of the blood volumes required, plus requirements for sample collection, handling and shipment to the assigned central laboratory, will be described in Laboratory Manual for the study.

6 STUDY MEDICATION AND ADMINISTRATION

Investigational Medicinal Product (IMP) will be provided by the Sponsor as summarized in Table 11 Both BGB324 and pembrolizumab will be labelled in compliance with GMP Annex 13 requirements or other applicable local regulatory guidelines.

Table 11: Product Descriptions

Product Name & Potency	Dosage Form
BGB324 100 mg	HPMC capsule
MK-3475 10 mL, 100 mg/vial (Liquid) (4 mL fill volume, 25 mg/mL potency)	Solution for Injection

6.1 Preparation and Dosing of Study Treatments

Further details on preparation and administration of both BGB324 and pembrolizumab are provided in the Pharmacy Manuals.

6.1.1 BGB324

BGB324 is provided in bottles containing a specified number of capsules per bottle to dispense to the patients. **Patients will be asked to take the specified number of capsules for their prescribed dose on an empty stomach at a regular time each day with water.** On pembrolizumab dosing days, patients will be asked not to take their BGB324 dose before coming into the clinic. On these days, pembrolizumab will be administered first, and the patient observed for 1 hour after the end of infusion (for infusion and other AEs), prior to taking their BGB324 dose (on an empty stomach and with water). Patients should not eat for at least one hour after taking BGB324.

6.1.2 Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg (two vials) given as a 30 minute i.v. infusion through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2-5 micron in-line or add-on filter. Dosing will be on Day 1 of each 3-week treatment cycle.

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted i.e. infusion time may be 30 minutes -5 min/+10 min.

6.2 Treatment Compliance

The patient will be asked to bring all bottles, including the empty ones, with them to each study visit to check compliance and for the Drug Accountability to be completed in the eCRF.

At each visit the Investigator or study staff will question the patient about the proper intake.

Proper intake, missed doses or failures in compliance will be recorded in the patient's file. The patient will be instructed as to the importance of taking their BGB324 in accordance with instructions.

6.3 Storage of Study Treatments

6.3.1 BGB324

BGB324 will be shipped to the site and must be stored at the site in a secure location under controlled, ambient temperature conditions (<25 °C or <77 °F). Instructions for the storage of dispensed BGB324 at home will be provided to every patient enrolled in the clinical study.

6.3.2 Pembrolizumab

Pembrolizumab (in 10 mL glass vials) will be shipped to the site and must be stored as follows:

- Cold storage (2 to 8 ^{o}C; 36 to 46 ^{o}F);
- Protect from light (a maximum of 24 hours exposure to light is permitted);
- Do not freeze;
- Do not shake.

6.4 Drug Accountability

The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the TMF.

The investigator is responsible for keeping accurate records of the clinical supplies received from the sponsor or designee, the amount dispensed to and returned by the patients and the amount remaining at the conclusion of the trial. For all trial sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction, if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/ destruction procedure is documented.

Certificates of delivery and return must be signed by the responsible pharmacist, and copies retained in the Pharmacy File.

The medication provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug to ensure that:

- deliveries of BGB324 and pembrolizumab are correctly received by a responsible person;
- such deliveries are recorded;
- study treatments are handled and stored safely and properly as stated on the label;
- study drug is only dispensed to study patients in accordance with the protocol; and
- any unused study drug is destroyed locally or returned for destruction in liaison with the study monitor.

6.5 Method of Enrolling Patient to Study Treatment

During Screening, patients will be allocated a unique patient number from the RAVE, once written informed consent has been obtained. Patients will continue to be identified by this number throughout the study. Once a Subject Number has been assigned, it cannot be used again.

6.6 Dose Modifications

Note: Three toxicities have been identified as potentially overlapping with both BGB324 and pembrolizumab – diarrhea, rash and renal toxicity. Please see Section 6.6.4 for the management of these toxicities.

Other toxicities can be managed as described in Section 6.6.1, Section 6.6.2 and Section 6.6.3.

6.6.1 BGB324 dose modification for toxicity

If a patient experiences drug related toxicity that requires treatment with BGB324 to be interrupted, a delay of up to 14 days is permitted to allow for resolution of toxicity. In the absence of recovery, treatment with BGB324 should be discontinued. See Table 12.

If treatment with BGB324 is interrupted, the relevant toxicity must have resolved to ≤Grade 1 or tolerable Grade 2 or baseline for treatment to recommence.

Only one dose reduction from 200 mg to 100 mg daily dose is possible.

Table 12: Dose Modification for BGB324-related Toxicity

Grade (CTCAE)	Recommended Dose Modification
Grade 1 and Grade 2 (tolerable)	
Any occurrence	Maintain dose of 200 mg if toxicity is tolerated by the patient
Grade 2 (intolerable)	
1st or 2nd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Resume dosing at 200 mg
3rd occurrence of same adverse event	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce to 100 mg
4th occurrence of same adverse event	Discontinue permanently
Grade 3	
1st occurrence	Interrupt treatment until toxicity returns to baseline, Grade 1 or tolerable Grade 2 Dose reduce to 100 mg or Discontinue permanently if dose has already been reduced
2nd occurrence of same adverse event at G3	Discontinue permanently
Grade 4	
1st occurrence	Discontinue permanently
Notes: • Treatment interruption for BGB324-related toxicity should be limited to 14 days • Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg BGB324) • Patients being considered for dose reduction or permanent discontinuation of BGB324, may be discussed with	

Grade (CTCAE)	Recommended Dose Modification
the Medical Monitor • Patients require an ECG twice weekly for the first 2 weeks after recommencing BGB324 following an interruption (see Section 5.3.9)	

6.6.2 BGB324 dose modification for QTc

Treatment with BGB324 produces QTc prolongation. In order to reduce the risk of QTc prolongation, all efforts should be made to maintain the patient's serum potassium levels at >4 mmol/L during treatment with BGB324 and for 2 weeks following completion of therapy (at an unscheduled visit, if required). Serum calcium and magnesium should be measured and reasonable efforts made to maintain at normal levels throughout treatment. Patients with an average QTc of ≥480 ms should be closely monitored until the QTc falls below 480 ms; electrolytes should be measured and corrected as necessary.

If a patient experiences QTc prolongation, BGB324 dosing should be reduced as outlined in Table 13. **Treatment with BGB324 should be permanently discontinued in the presence of ventricular arrhythmia.**

Table 13: Dose modification of BGB324 for QTc Prolongation

QTcF	Recommended BGB324 Dose Modification
Grade 1 (450-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms) - on two consecutive occasions per protocol assessments or investigator's judgement	
1st occurrence	Interrupt treatment with BGB324: i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, restart BGB324 at a reduced dose of 100mg or discontinue if no further dose reduction is possible. ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, discontinue BGB324 permanently.
≥2nd occurrence (following a previous dose reduction for QTcF)	Discontinue BGB324 permanently.
≥Grade 3 (≥501 ms)	
1st occurrence	Interrupt treatment with BGB324: - if QTcF reduces to ≤Grade 1 by 14 days from initial recording, restart BGB324 at a reduced dose of 100mg or discontinue treatment if dose reduction is not possible - if QTcF does not reduce to ≤Grade 1, discontinue BGB324 permanently.
2nd occurrence	Discontinue BGB324 permanently
Ventricular arrhythmia	
1st occurrence	Discontinue BGB324 permanently
Notes: • Serum calcium, magnesium and potassium should be measured regularly whilst receiving BGB324; all abnormal results should be corrected • The mean QTcF value from triplicate ECG readings should be used when considering dose modification	

QTcF	Recommended BGB324 Dose Modification
• Treatment interruption for BGB324-related toxicity should be limited to 14 days • Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg BGB324) • Patients being considered for dose reduction or permanent discontinuation of BGB324 may be discussed with the Medical Monitor • Patients require an ECG twice weekly for the first 2 weeks after recommencing BGB324 following an interruption (see Section 5.3.9)	

6.6.3 Pembrolizumab dose modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 14 below. See Section 6.11 for supportive care guidelines, including use of corticosteroids.

Table 14: Dose modification guidelines for pembrolizumab drug-related adverse events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4 or Recurrent 2	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; **Refer to Section 6.12, Table 18 – Infusion Treatment Guidelines for further management details**.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

6.6.4 Dose modifications for BGB324 and pembrolizumab for overlapping toxicities

Three toxicities are identified as potentially overlapping with both BGB324 and pembrolizumab: diarrhea, rash (including dermatitis, pruritus) and renal toxicity (renal failure, serum creatinine elevation, nephritis).

See also, Supportive Care Guidelines for Pembrolizumab – Section 6.11.

6.6.4.1 Dose modifications for diarrhea

Patients may continue with baseline anti-diarrheal medications throughout treatment with pembrolizumab. If a patient experiences an increase in diarrheal symptoms after starting BGB324 they may increase the dose of anti-diarrheal medication such as loperamide during the first week of treatment only. Starting treatment with loperamide is also acceptable during this period. Thereafter any increased diarrheal symptoms should be reported to the investigator immediately and further medication should not be given. See Table 15.

Table 15: Pembrolizumab and BGB324 Dose Modification for Diarrhea

Diarrhea with onset in the 2nd cycle or later cycle	Pembrolizumab	BGB324
Grade 2-3	Withhold for up to 12 weeks of last dose • If resolved to Grade 0 or 1, restart pembrolizumab • Permanently discontinue if not resolved to grade 0 or 1, or, there is an inability to reduce corticosteroid to ≤10 mg (prednisone or equivalent) per day	Withhold for up to 14 days • If resolved to grade 0 or 1, restart BGB324 at 100 mg qd • Permanently discontinue if not resolved to grade 0 or 1
Grade 4	Permanently discontinue	Permanently discontinue

6.6.4.2 Dose modifications for rash (including dermatitis, pruritus) – Table 16

Table 16: Pembrolizumab and BGB324 Dose Modification for Rash

Rash – onset during any cycle	Pembrolizumab	BGB324
Grade 2	Pembrolizumab can continue as scheduled	BGB324 can continue as scheduled
Grade 3 or severe	Withhold for up to 12 weeks of last dose • If resolved to grade 0 or 1, restart pembrolizumab • Permanently discontinue if not resolved to grade 0 or 1, or, there is an inability to reduce corticosteroid to ≤10 mg (prednisone or equivalent) per day	Withhold for up to 14 days. • If resolved to grade 0, 1 or tolerable grade 2, restart at 100 mg qd • Permanently discontinue if not resolved to grade 0, 1 or tolerable grade 2
Grade 4	Permanently discontinue	Permanently discontinue

6.6.4.3 Dose modifications for renal toxicity (renal failure, serum creatinine elevation, nephritis) – Table 17

Table 17: Pembrolizumab and BGB324 Dose Modification for Renal Toxicity

Renal failure, serum creatinine elevation, nephritis – onset during any cycle	Pembrolizumab	BGB324
Grade 2	Withhold for up to 12 weeks of last dose • If resolved to grade 0 or 1, restart pembrolizumab • Permanently discontinue if not resolved to grade 0 or 1, or, there is an inability to reduce corticosteroid to ≤10 mg (prednisone or equivalent) per day	Withhold for up to 14 days • If resolved to grade 0 or 1, restart at 100 mg qd • Permanently discontinue if not resolved to grade 0 or 1
Grade 3	Permanently discontinue	Withhold for up to 14 days • If resolved to grade 0, 1 or tolerable grade 2, restart at 100 mg qd • Permanently discontinue If not resolved to grade 0, 1 or tolerable grade 2
Grade 4	Permanently discontinue	Permanently discontinue

6.7 Blinding and Procedures for Un-Blinding the Study

This is an open-label study, and there are no blinding/un-blinding procedures.

6.8 Permitted and Restricted Concomitant Medications

In general, medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Treatment with antacids, proton pump inhibitors and histamine receptor 2 inhibitors can be initiated as rescue therapy after patients have been receiving BGB324 for one week, provided they are taken in the evening.

If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy or vaccination schedule (see Section 6.10) requires the mutual agreement of the investigator, the Sponsor and the patient.

Patients should not receive BGB324 during periods of systemic corticosteroid treatment. If a patient requires treatment with systemic corticosteroids, BGB324 should be interrupted immediately. Treatment with BGB324 may be restarted upon completion of systemic corticosteroid therapy. BGB324 may be continued at the appropriate dosage during periods of topical and inhaled corticosteroid therapy.

Hormonal contraception for female breast cancer patients is contraindicated.

6.9 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter, herbal supplements, and i.v. medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interest (ECIs) as defined in Section 7.4.3.2.

6.10 Prohibited Concomitant Medications Whilst Receiving Pembrolizumab

Patients are prohibited from receiving the following therapies during the Screening and Treatment period (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than BGB324 and pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor.

The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS. *Note: Treatment with pembrolizumab and BGB324 must have been discontinued at least one week prior to radiotherapy and should not be restarted within one week of completing radiotherapy.*

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. If a patient requires physiologic doses of corticosteroids, they must discontinue their BGB324.
  - Note: Inhaled steroids are allowed for management of asthma.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Follow Up period once the patient has discontinued both treatments.

6.11 Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Patients receiving oral or intravenous corticosteroids must interrupt treatment with BGB324 throughout the duration of therapy.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.6 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events and **Grade 2-4** hypothyroidism:

        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with i.v. corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

6.12 Infusion Guidelines for Pembrolizumab

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 18 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 18: Management of pembrolizumab-associated infusion-related reactions

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to:	Patient may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
indicated for <=24 hrs	• IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be pre-medicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.13 Diet, Activity and Other Considerations

6.13.1 Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.14 Contraception

Pembrolizumab and BGB324 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient AEs on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

- postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high FSH level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

- have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

- has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree use highly effective methods of contraception while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following highly effective methods‡:

- intrauterine device (IUD);
- intrauterine hormone-releasing system (IUS);
- bilateral tubal occlusion;
- vasectomized partner;
- practice abstinence from heterosexual activity†

Note: hormonal contraceptives are normally contraindicated in female patients with breast cancer.

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Board (IRB)/Institutional Ethics Committee (IECs). Periodic abstinence e.g. calendar, ovulation, sympto-thermal, post-ovulation methods, etc. and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6.14.1 Use in pregnancy

If a patient inadvertently becomes pregnant while on treatment with study medication, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

6.14.2 Use in nursing women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrolment.

7 ADVERSE EVENTS AND REPORTING REQUIREMENT

7.1 Assessment of Safety

Progression of the cancer under study is not considered an AE unless it is considered to be drug-related by the investigator.

All **AEs that occur after the consent form is signed but before treatment allocation** must be reported by the investigator if they cause the patient to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation through 30 days following cessation of treatment, all AEs must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets.

The reporting timeframe for AEs meeting any serious criteria is described in Section 7.4.3. The investigator will make every attempt to follow all patients with non-serious adverse events for outcome. **From the time of treatment allocation through 90 days following cessation of treatment, all SAEs (including serious events of special interest) must be reported by the investigator.** Where a patient has initiated a new cancer treatment, the time period is 30 days after cessation of treatment. See Section 7.4.3.1 and Section 7.4.3.2.

The reporting timeframe for a new pregnancy is described in Section 7.5.

7.2 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable or unintended sign, symptom or disease temporally associated with the use of the IMP whether or not considered related to the IMP. This includes any occurrence that is new, an exacerbation of an existing disease (a worsening of the character, frequency or severity of a known condition) or abnormal results of diagnostic procedures, including clinically significant laboratory test abnormalities.

Suggested criteria for the assessment of clinical significance for laboratory abnormalities are as follows.

The laboratory abnormality:

- is clearly consistent with the pattern of the patient's underlying disease or disease progression;
- is accompanied by clinical symptoms;
- requires study drug dose modification or interruption or permanent discontinuation of study treatment;
- requires more frequent follow-up assessments, further diagnostic investigation, etc.;
- requires a change in concomitant medication, therapy, or treatment.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g. alkaline phosphatase and bilirubin 5X ULN associated with cholecystitis), only the diagnosis (e.g. cholecystitis) needs to be recorded on the AE CRF. If the clinically significant laboratory

abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. 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 as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

For all AEs, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases) wherever possible. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single syndrome at the time of reporting, each individual sign and/or symptom should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, the reported event term should be updated to reflect the medical diagnosis.

Note that AEs occurring secondary to an initiating event that are separated in time or medically significant should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to a renal failure, both events should be recorded separately on the CRF.

A pre-existing medical condition which is present at the start of the study and described in the Medical History CRF, should only be recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g. "more frequent headaches").

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. To prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

Symptoms and signs of exacerbation or worsening of the patient's primary disease will not be captured as AEs. Progression of the disease under study (i.e. TNBC) will not be captured as an AE unless it is considered to be drug-related by the Investigator.

7.3 Importance of Adverse Event Reporting

Timely and complete reporting of safety information assists BerGenBio in identifying any untoward medical occurrence, thereby allowing:

- safety of study patients;
- a greater understanding of the overall safety profile of the investigational drug;
- recognition of dose-related investigational drug toxicity;
- appropriate modification of study protocols;
- improvements in study design or procedures; and

- adherence to worldwide regulatory requirements.

7.4 Evaluating Adverse Events

Following the patient's written consent to participate in the study, AEs occurring after consent, but before treatment, and during treatment and within 30 days after cessation of treatment are collected in accordance with Section 7.1, Section 7.4.3 and Section 7.5.

All identified AEs must be accurately recorded and described on the appropriate AE page of the electronic Case Report Form (eCRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: date of onset and resolution, severity of the event (see definitions in Section 7.4.1), Investigator's opinion of the relationship to IMP (see definitions in Section 7.4.2), and assessment whether the event was serious or non-serious (see definitions in Section 7.4.3). In addition, treatment required for the AE, action taken with IMP, information regarding resolution/outcome.

7.4.1 Assessment of severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's eCRF. Each event will be graded for severity using the classifications of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For events not addressed in the NCI CTCAE v4.03, classifications the following grading will apply:

- **Mild (Grade 1)** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)** - Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- **Severe (Grade 3)** - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)** - Related to adverse event.

7.4.2 Assessment of relationship

All AEs (including SAEs) will be assessed for the relationship of the AE to both pembrolizumab and BGB324 study drug using the following definitions:

- **Not/unlikely related** - The AE is not related if exposure to the investigational product has not occurred, *OR* the occurrence of the AE is not reasonably related in time, *OR* the AE is considered unlikely to be related to use of the investigational product because there are no facts (evidence) or arguments to suggest a causal relationship *AND* there is a possible alternative explanation.
- **Possibly related** - The administration of the investigational product and AE are considered reasonably related in time *AND* the AE could be explained by causes other than exposure to the investigational product.

- **Probably related** - Exposure to the investigational product and AE are reasonably related in time *AND* the investigational product is more likely than other causes to be responsible for the AE *OR* is the most likely cause of the AE.
- **Definitely related** - There is a reasonable temporal sequence between exposure to the investigational product and the AE, *OR* the event follows a known or expected response pattern to the investigational product, *AND* is confirmed by improvement on stopping the dosage of the investigational product. It may also be confirmed by reappearance upon repeated exposure where this is medically and ethically acceptable.

The relationship of the study treatment to an AE will be determined by the Investigator and subsequently reviewed by the Medical Monitor.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor's Medical Monitor, the more conservative assessment will determine the reportability of the case.

7.4.3 Immediate reporting of adverse events and events of clinical interest to the Sponsor

7.4.3.1 Serious adverse events

An **SAE** is any untoward medical occurrence that at any dose (including overdose):

- Results in death.
- Is life-threatening:
  - "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization:
  - This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.
  - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfils any other of the serious criteria.
- Results in persistent or significant disability or incapacity:
  - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event:
  - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed

in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per International Conference Harmonisation (ICH) definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment allocation, any SAEs, or follow up to a SAE, including death due to any cause other than progression of the cancer under study, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All patients with SAE must be followed up for outcome.

7.4.3.2 Events of clinical interest

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

ECIs for this trial include:

- an overdose of Sponsor's product (either pembrolizumab or BGB324), as defined in Section 7.8, that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Guidance for Potential Drug-Induced Liver Injury (DILI) Cases Meeting Hy's Law Criteria held in the Investigator Trial File Binder (or equivalent).

7.5 Reporting SAEs and ECIs

Adverse events classified as SAEs or ECIs must be recorded on the designated eCRF page and require expeditious handling and reporting to the Drug Safety group at INC to comply with regulatory requirements.

The Principal Investigator (or designee) will notify INC within 24 hours of identifying an SAE or ECI, whether related or unrelated to investigational drug, by completing the SAE form and faxing the eCRF pages and any available supporting documentation to INC (see Table 19 below for contact details).

When an overdose or drug misuse of either of the investigational products occurs with an adverse outcome, the Investigator should only complete the designated AE or SAE eCRF page. Expeditious handling and reported may be appropriate.

In the case of pregnancy, a separate 'pregnancy' and 'pregnancy outcome' form is used. However, the patient should be withdrawn from study treatment and appropriate follow up agreed with the Sponsor.

Table 19: Contact Details for SAE, ECI, New Cancer and Pregnancy/Lactation Reporting

Drug Safety CRO:	INC Research 3201 Beechleaf Court Suite 600 Raleigh, NC 27604 USA
SAE Facsimile Transmission:	Each country will have a dedicated specific toll free fax number. A general toll fax number is provided below; whilst the list of countries with the dedicated toll-free fax numbers will be provided on the SAE cover page. 1-877-464-7787 (US/Canada toll free fax number and Global toll fax number)
SAE e-Mail Contact: INC	INCDrugsafety@INCResearch.com

7.6 Assessment of Expected Adverse Events

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event considered to be at least possibly related to BGB324 or pembrolizumab where the outcome, specificity, or severity of which is not consistent with those noted in the current IB for BGB324, or the SmPC or Prescribing Information for pembrolizumab.

7.7 Reporting of Pregnancy or Lactation

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the patient to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of first dose of study treatment through to 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (as Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pregnancies are to be reported using the same procedures/transmission methods as SAEs: the same fax numbers/email address / same SAE cover sheet. A study specific pregnancy form will be provided for pregnancy reporting.

7.8 Definition of Misuse and Overdose

BGB324 overdose is defined as any dose level administered which exceeds the assigned study dose level (including dose reductions).

For this trial, a pembrolizumab overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If the pharmacy discovers that an overdose has or may have been administered, they should contact the Study Investigator immediately. The Study Investigator will determine if the overdose is an Event of Clinical Interest (see Section 7.4.3.2).

7.9 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the Sponsor immediately. The same reporting timelines as for SAEs apply.

7.10 Reporting SAES to the IRB or IEC

The Investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB or IEC. All SAEs that are related and unexpected must be reported by the Investigator (or alternative responsible person where specified in study delegation log) to the IEC/IRBs responsible for the study.

In such cases, the Drug Safety group will send the Principal Investigator a Council for International Organizations of Medical Sciences (CIOMS) or MedWatch form describing the event, for them to report to their IEC/IRB.

Other SAEs (i.e. expected or unrelated SAEs) should be reported per the relevant institution's procedures.

The Principal Investigator should also comply with the IEC/IRB procedures for reporting any other safety information. Periodically (at least annually), the IB will be updated to include new and relevant safety information.

Until such time that an AE becomes identified in the BGB324 IB, it should be considered unexpected in regard to BGB324 causality, regardless of whether the AE has been the patient of a previous Safety Update.

7.11 Follow Up Information on an SAE

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report. The original SAE form(s) must be kept on file at the study site. The Sponsor will also review SAE reports for missing information and send queries to the site for resolution as appropriate.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Principal Investigator (or designee). An SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, or is explained by the Principal Investigator.

7.12 Sponsor Reporting of SAEs

The Sponsor is responsible for reporting serious, study drug–related AEs to the Competent Authorities of the countries participating, the Central IRBs/IECs participating in the clinical trial and to the study Investigators. The Sponsor has assigned the drug safety group at INC Research to act on their behalf for safety submissions on this clinical study.

The Sponsor (or their delegated Medical Monitor) will determine whether expedited reporting is necessary for SAEs depending on the assessment of seriousness, expectedness, and relationship. In case of disagreement between the Investigator and the Sponsor's Medical Monitor regarding causal relationship, the more conservative assessment will determine the reportability of the case.

The Sponsor, or their delegated Clinical Research Organization (CRO), will prepare Development Safety Update Reports (DSUR) and send the DSUR to the European Competent Authority(ies) and the US Authority(ies) where the trial is approved within the regulatory timeframe appropriate for the outcome of their assessment (see Section 7.12.1 and Section 7.12.2). The assigned CRO will send the DSUR to the concerned IRB/IECs.

7.12.1 Expedited reporting

The Sponsor (or delegate) is responsible for the ongoing safety evaluation of the IMP. The assigned drug safety group is responsible for ensuring that expedited reports are made to all concerned Investigators, to the concerned IRB/IECs (where required), and to the relevant regulatory authorities of all adverse drug reactions that are both serious and unexpected, and of findings that could adversely affect the health of patients, impact on the conduct of the trial, or alter the Competent Authority's authorization to continue the trial.

In accordance with the US Code of Federal Regulations, Title 21 CFR Part 312.32, the European Directive 2001/20/EC, and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an Investigational new drug (IND) Safety Report or suspected unexpected serious adverse reaction (SUSAR) reports, respectively. The Sponsor should submit to the Regulatory Authority all safety updates and periodic reports, as required by applicable regulatory requirements.

The drug safety group will assign a case number to be used in all future correspondence regarding the event.

All events qualifying as IND Safety Reports/SUSARs will be reported to the relevant regulatory authorities, IRB/IECs, and Investigators by the drug safety group. IND Safety Reports/SUSARs are required to be reported within 7 calendar days for life-threatening events and those resulting in death or 15 calendar days for all others. These timeframes begin with the first notification of the IND Safety Reports/SUSARs to the drug safety group from the Investigator.

7.12.2 Non-expedited reporting

All SAEs that do not require expedited reporting will be described in the interim safety reports.

8 DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

8.1 Statistical Considerations, Interim Analysis and Sample Size

The study will employ a *k*-stage single arm design, an approach derived from basic statistical theory[23]. If p denotes the true tumor response rate with drug, the null and alternative hypotheses to be assessed in this trial are: H_0 : RR=p_0 vs H_1 : RR=p_1 (p_0 <p_1), with p_0=0.20 and p_1=0.35. To test these hypotheses, this trial is a *k*-stage single arm design with *k*=2, being an extension of Simon's 2-stage design[1]. In this design with *k*=2, there are two analyses: a single interim and a final analysis. At the interim, the response rate is evaluated in a fixed number (*m*) of patients using a predefined decision rule to determine if the study should stop for futility (in the situation where the null is confirmed) or for efficacy (in the situation where the alternative hypothesis is confirmed). If neither hypothesis is confirmed, a further fixed number of patients (*l*) are assessed for response and a final analysis is performed on all (*m*+*l*) patients. In both interim and final analyses, the response rate will be presented together with the associated exact 90% confidence interval (CI).

With p_0=0.20 and p_1=0.35, the interim will be conducted with *m*=28 patients. If 5 or fewer responses are observed in these 28 patients, the trial will be terminated in favor of the null for futility; however, if 11 or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Otherwise a further 28 patients may be evaluated, for a total of 56 patients. If a total of 17 or more responses are seen in 56 patients, then the null will have been rejected in favor of the alternative; otherwise the null will not have been rejected.

Based on 500,000 trial simulations, this design provides an overall power of 80.6% to test the stated null and alternative hypothesis with a 1-sided Type I error rate of 0.048. Under the null hypothesis, the probability of correctly stopping for futility at the interim is 50.2% and, under the alternative hypothesis, the probability of correctly stopping for activity at the interim is 38.4%. Consequently, the expected sample size for the design is 42-44 subjects.

8.2 Data Review Committee

8.2.1 Safety Run-In

Pembrolizumab has not previously been combined with BGB324 in patients (in any indication) and therefore, a safety run-in will include a total of 12 patients.

A Data Review Committee (DRC), consisting of Principal Investigators, the Sponsors' (BerGenBio and Merck) Medical Monitors, and invited experts as required, will review all patient safety data after 6 patients have been enrolled and had the potential to be followed for 6 weeks (2 cycles), and then again after a further 6 patients (total 12 patients) have had the potential for 6 weeks follow-up. At each of these safety reviews, the DRC will consider the rate of BGB324 dose reductions and the rate of permanent discontinuation from BGB324 and pembrolizumab.

Each patient will have had the potential to receive (as a minimum):

- 2 cycles of pembrolizumab
- BGB324 at 400 mg for 3 days, followed by 200 mg daily for ~6 weeks

At the 1st safety run-in (based on 6 patients) the DRC will evaluate the need for dose modification for individual patients, or BGB324 loading or daily dose modification. A rate of >66% (4 or more) of patients requiring treatment to be dose reduced (BGB324) or permanently discontinued (either BGB324 or pembrolizumab, or both) will considered as a significant rate.

The 2nd safety run-in (based on the 12 patients) the DRC will again evaluate the need for dose modification for individual patients, or BGB324 loading or daily dose modification. A rate of >40% (5 or more) of patients requiring treatment to be dose reduced (BGB324) or permanently discontinued (either BGB324 or pembrolizumab, or both) will considered as a significant rate.

During the safety run-in reviews, the DRC will have the option to recommend a lower dose of BGB324 (dose level -1) for new patients. Dose level -1 is defined as 200 mg BGB324 on Days 1, 2 and 3 followed by 100 mg from Day 4 onwards.

Additionally, a review of emerging safety data from the whole BGB324 program will be made 6-monthly.

8.2.2 End of Stage 1 – Efficacy Analysis

Recruitment to the study will be halted once 28 evaluable patients have been entered, and whilst the Stage 1 analysis is conducted. Recruitment will recommence if the decision is made to continue to the maximum of 56 evaluable patients.

The DRC will meet to review the overall risk/benefit profile of the combination, together with the ORR when 28 patients have had the potential to be followed for 24 weeks – and therefore these patients have the potential to have data from at least 2 post-treatment tumor-imaging assessments. The DRC will document the ORR and if it favors the null hypothesis for futility, or the alternative hypothesis for demonstration of activity, and recommend if the study should proceed to evaluate up to a further 28 patients. This recommendation will take into account the statistically-driven endpoint, in the context of on-going safety data review of the combination approach, as well as the quality of the response e.g. available data on duration of response (DoR) and progression-free survival (PFS), where possible.

Appropriate representatives of the Sponsor and the coordinating personnel may also attend and minute DRC meetings. Recommendations of the DRC will be documented and sent to the sites. Further details on the composition of the DRC, as well as the process for data review, issue of recommendations and decision making, are described in a separate DRC charter for this study.

8.3 Statistical Analysis Plan

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will detail all data handling rules e.g. full definition of patient populations for analysis, including the management of missing values and the handling of data for patients lost to follow-up or missing other important information. The SAP will also outline protocol deviation criteria. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report. It will also describe the rules the handling of missing data points for the primary, secondary and exploratory endpoints.

An interim analysis will be performed after 28 evaluable patients have had the potential to have at least 24 week follow-up (enabling each patient to have the potential for at least 2 'on treatment' disease assessment scans). Recruitment will be halted during this period and until the interim analysis has been conducted.

The SAP will fully describe the efficacy analyses and descriptive summaries that will be undertaken for both the interim and final analyses. All efficacy endpoints (ORR, DoR, PFS, DCR and OS) will be summarized and described for both the interim and final analyses. See Section 8.11 and Section 8.12 for further details.

Summaries of ORR by PD-L1 and Axl expression will be provided for both the interim and final analyses.

The clinical database lock for the final analysis will occur after the final patient has had the potential to be followed for 24 weeks and after all data are reconciled (i.e. "cleaned") for all patients who participate in the study. A single clinical study report (CSR) will be generated. The SAP will be finalized and signed before the database lock.

An addendum (or addenda) to the CSR will be generated to report SAEs from patients remaining on treatment at the time of the LPLV patients to closure of the study (defined as every patient completing their study combination treatment) (Section 8.6).

The main data analyses intended for this trial are briefly described in this section and in Section 8.11 and Section 8.12. The SAP will provide full details of all planned data analyses for the primary, secondary and exploratory objectives of the study.

8.4 Population

The efficacy objectives will include all evaluable patients. An evaluable patient will have received at least one combination dose and who have measurable disease at entry according to the Investigator Site assessment.

For all safety objectives, the safety set consisting of all patients that have received at least one dose of BGB324 and/or pembrolizumab will be used.

For some objectives (PK and biomarker) a subgroup of patients of the safety set with respective baseline and post-baseline measurements will be used.

Patients who signed a consent form and were screened but did not receive any treatment will be listed if they reported an AE in the time after consent and before treatment allocation (Section 7.1). All AEs that occur after the consent form is signed but before treatment allocation must be reported if they cause the patient to be excluded from the trial, or are result of protocol-specific intervention, including but not limited to, washout or discontinuation of usual therapy, diet, placebo treatment or a procedure (Section 7.1).

8.5 RECIST 1.1 and Disease Assessment

Efficacy endpoints in this study, including ORR, DoR, PFS will all be based on tumor imaging evaluation by RECIST 1.1[2].

RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of chest, abdomen, and pelvis. Additionally, x-ray, bone scans and brain scans will be used as appropriate.

Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment (although bone scans and brain scans may be done within 6 weeks), and ideally should be performed as close as possible to the start of study treatment.

All radiological and non-radiological (eg, MRI) scans will be reviewed by the local site investigator; and if possible, stored electronically (de-identified with the patient's notes) at site.

A maximum of 5 target lesions must be selected at baseline. All target lesions are measurable. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements.

All remaining lesions present at baseline are considered non-target, irrespective of whether they are measurable.

Disease assessments will be performed every 9 weeks ±7 days for the first 46 weeks relative to the date of first treatment administration and then every 12 weeks ±7 days thereafter until confirmed objective disease progression as defined by RECIST 1.1[2] (irrespective of the reason for stopping treatment or subsequent therapy).

Any other sites at which new disease is suspected should also be adequately imaged at follow/up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Table 20 provides the RECIST 1.1[2] evaluation and definitions of disease response (based on TLs).

Table 20: RECIST 1.1 evaluation and definitions of disease response

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs and an absolute increase of at least 5 mm, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response

All patients who are considered to have had a complete or partial response must have this response confirmed by a confirmatory scan at least 4 weeks later.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression, however, in the absence of clinical deterioration, treatment can continue. The suspected disease progression should be confirmed after 28 days.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Disease progression requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of progression of disease (PD) in the absence of clinical deterioration.

The overall visit response will be derived using the algorithm shown in Table 21.

Table 21: Overall visit response algorithm

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No or NE	CR
CR	NA	No or NE	CR
CR	Non CR/Non PD	No or NE	PR
CR	NE	No or NE	PR
PR	Non PD or NE or NA	No or NE	PR
SD	Non PD or NE or NA	No or NE	SD
NE	Non PD or NE or NA	No or NE	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no non-target lesions at baseline).

8.5.1 Immune-related RECIST 1.1 and confirmation of progression

RECIST 1.1[2] will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1[2] will be used with the following adaptations:

If radiologic (or non-radiological) imaging suggest that the patient has progressive disease (initial PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

- If repeat imaging shows <20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed;
- If repeat imaging confirms PD due to any of the scenarios list below, patients will be discontinued from study therapy.

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥20% and at least 5 mm absolute increase compared to nadir;
- Non-target disease resulting in initial PD is worse (qualitative);
- New lesion resulting in initial PD is worse (qualitative);
- Additional new lesion(s) since last evaluation.

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression;
- No decline in ECOG PS;
- Absence of rapid progression of disease;
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

When feasible, patients should not be discontinued from their study treatment until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

8.6 Completion and Closure of the Study

The study will be completed when either:

- The study is terminated at the interim analysis following the DRC review of the ORR and risk/benefit for all patients included in the interim analysis. In this (early termination) situation a Clinical Study Report will be written. The interim analysis will occur once 28 evaluable patients have had the potential to be followed for at

least 24 weeks. In this situation, the last patient, last visit (LPLV) will occur at this point.

OR

- The study will complete and the final analysis will occur once all patients (planned 56 evaluable patients) have had the potential to be followed for at least 24 weeks. The last patient, last visit (LPLV) will occur at this point. All data will be reconciled and the database will be locked for analysis. These data will be included in the CSR.

Assuming that there are patients continuing on study treatment at the date of LPLV, the study will be closed once all patients have completed their last dose of study drug or discontinued study drug and have completed their post treatment visit.

- If this closure date occurs after the date of LPLV, only serious safety data will be collected between LPLV and the final closure date. An addendum (or addenda) to the CSR will be generated to report any outstanding serious safety data.
- If this 'closure date' occurs before the date of LPLV (because every patient has stopped their study treatment, for example), the study will close at the same time as the date of LPLV.

Study start is defined by the first patient to enter screening, however, the First Patient In (FPI) is when the first patient receives the first dose of study drug.

LPLV is defined as the last visit after all evaluable patients who have had the potential to be followed for at least 24 weeks and includes all data for the final analysis of all evaluable patients.

Study Completion is defined by the date of the LPLV i.e. after the planned number of evaluable patients have had the potential to be followed for at least 24 weeks.

Study Closure is defined by completion of the last dose of study drug and post treatment visit i.e. when the last patient has completed the last dose of study drug or discontinued for any reason and been followed up to the Post Treatment Visit. This date will either be the same as the date of Study Completion or later in time.

8.7 Demographic, Medical History, Prior Medication and Other Baseline Characteristics

Demographic characteristics, medical history, prior medication and other baseline data will be listed and summarized using descriptive statistics for continuation data and contingency tables for categorical data. Prior medication will be summarized by anatomical therapeutic chemical (ATC) terms.

8.8 Study Treatment

The number of doses of BGB324 and pembrolizumab by cycle and over entire study period will be listed and summarized using descriptive statistics. The time on study drug until last treatment received will be listed and presented by descriptive statistics.

8.9 Concomitant Medication

Concomitant medication and significant non-drug therapies after the start of study treatment will be listed and summarized by ATC term in contingency tables.

8.10 Reasons for Discontinuation from Study Treatment

Reasons for discontinuation of study treatment(s) will be listed and summarized.

8.11 Primary Objectives

Objective response rate as defined by achieving complete response and/or partial response will be presented by percentage rates and 90% CIs. All response assessments will be listed.

Note that the Disease Assessment time point used for this analysis may vary, and need not be the first on treatment assessment. Where there is the possibility of an immune response leading to a false categorization of disease progression, results from later tumor imaging time points may be used for the ORR assessment following the *k*-stage design.

Objective response rate is defined as the percentage of patients with a CR or PR (out of the number evaluable), a 90% CI for the overall ORR will be calculated assuming an exact binomial distribution.

A patient who has discontinued both treatments, and subsequently responds having received a subsequent anti-cancer treatment may be excluded (at the statistical analysis) from the subset of responding patients (these patients are evaluable, and will be included in the denominator). Such patients will contribute to the time to progression and death Kaplan Meier plots.

All patients with a documented PR or CR are expected to have the result confirmed by repeat scan at least 4 weeks (28 days) later.

The ORR will further be explored as follows:

- By PD-L1 status (+ve/-ve), using a Chi square or Fishers Exact Test
- By Axl status (+ve/-ve), using a Chi square or Fishers Exact Test, and
- Summarized in a table of PD-L1 by Axl expression status to explore the ORR in each of the four quadrants (++, +-, -+, --). That is, patients will be allocated into one of the 4 groupings: where both Axl and PD-L1 are positive; where there is one positive and one negative and where there are both Axl and PD-L1 negative.

If the PD-L1 expression status is provided as a TPS or, in one of 3 categories usually <1%, 1-49% and ≥50%, the patient will be regarded as PD-L1 positive if their TPS is ≥1%.

A patient with Axl positive disease is defined as one with an expression level of 1+ or greater according to IHC staining intensity, although other cut offs may be considered.

For each patient, the best percentage change in tumor volume will be illustrated in a 'waterfall' plot.

8.12 Secondary Objectives

8.12.1 Safety

8.12.1.1 Adverse event

Adverse events will be coded as described in Section 8.4. The number of AEs occurring at least once in a patient will be listed and summarized by contingency tables for:

- primary system organ class, preferred term;
- preferred term;
- NCI CTCAE grade;
- relationship to both study drugs;
- interruption of study drug;
- leading to discontinuation;
- Grade 3 and higher;
- SAEs;
- AEs leading to death;
- standard medical queries.

8.12.1.2 Safety laboratory

Laboratory values will be graded by NCI CTCAE version 4.03; if no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit and change from baseline values at each visit. Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

8.12.1.3 Vital signs

Vital signs will be summarized by descriptive statistics at each visit, change from baseline will be presented and a listing will be provided.

8.12.1.4 Electrocardiogram

ECG data will be listed overall and a separate listing for any clinical significant finding in ECG values will be provided.

8.12.2 Efficacy

8.12.2.1 Duration of response

The duration of response (DoR) will only be calculated for patients that have an objective response. The duration of response is calculated from the date of the first documented response until the date of progression or death; patients who continue to respond at the date of data cut-off (last patient last visit) will be censored using the same date used to censor for the progression free survival time. Median DoR and respective 95% CIs will be presented.

8.12.2.2 Disease control rate

Disease control rate (DCR) is defined as the percentage of patients with a PR, CR or with stable disease (out of number evaluable). A 95% CI for the DCR will be calculated using an exact binomial distribution.

A Kaplan Meier plot of the duration of response will be presented along with the median duration of response. Descriptive statistics will be used as required, including 95% CIs.

8.12.2.3 Progression free survival and overall survival

Kaplan Meier plots of the time to progression and death will be presented, along with the median progression free survival and the estimated survival at 12 months. Descriptive statistics will be used as required, including 95% CI.

PFS is measured from the date of the 1st dose of the 1st cycle until the date of progression (the date on which the progression is initially observed) or the date of death (whichever is earlier). Patients who have not progressed or died before the date of data cut-off (last patient, last visit) will be censored at their last clinical evaluation.

The estimated survival at 12 months will be read from the Kaplan Meier OS curve. The time to death is defined as the time from the date of enrolment until the date of death (from any cause and irrespective of any subsequent ant-cancer treatment given). Patients who remain known to be alive at the date of data cut-off (last patient, last visit) will be censored at their date last known to be alive. Patients who are lost to follow-up will be censored at the point last known to be alive; however, if ≥2% of patients are in this category, a sensitivity summary will be produced to illustrate the overall survival assuming the patient died at the date last known in the trial. If possible, the date of death may be recovered from publically available sources such as death registries.

8.12.3 Pharmacokinetics

The analysis plan for PK assessment for BGB324 in the study will be part of the SAP. PK parameters (see Table 22) will be estimated for each patient using a fully validated version of WinNonlin Pro (Version 6.3 Phoenix™, Pharsight®), or later version as appropriate. The following parameters will be derived for BGB324, where appropriate, from the individual plasma concentration versus time profiles from all patients.

Blood samples taken for the purpose of PK assessment of pembrolizumab will be frozen and stored in case they are required in the future (for example, at the request of a regulatory authority).

Table 22: Pharmacokinetic parameters

Parameter	Definition
C_{max}	The maximum observed concentration.
t_{max}	The time at C_{max}
$AUC_{0\text{-}24h}$	The area under the concentration versus time curve from time zero to 24 h post-dose; that is, within a dosing interval
C_{av}	Average concentration calculated as $AUC_{0\text{-}24h}/24$
$t_{1/2}$	The elimination half-life

Blood samples taken for the purpose of PK assessment of pembrolizumab will be frozen and stored in case they are required in the future (for example, at the request of a regulatory authority).

8.13 Exploratory Objectives

8.13.1 Biomarker analysis

The PD-L1 and Axl expression status will be available at the time of the database lock and will be utilized in the analysis of the study, as described in Section 8.11.

However, results from other biomarkers (for example, for the assessment of Axl inhibition and signaling) may not be available at the time of the interim analysis clinical database lock, but are intended to be completed before the closure of the study or before the clinical study report is written at study completion (whichever is later) – see Section 8.6. A separate analysis plan and report (addendum to the CSR) for biomarker analysis will be written. All samples will be destroyed within 5 years of the last patient being entered to Stage 1.

9 QUALITY ASSURANCE

9.1 Data Recording

The Investigator will be responsible for the recording of all data on the CRFs provided, as certified by the Investigator's signature and date on the designated pages. All study data will be collected using an eCRF within a fully validated and CFR 21 Part 11-compliant electronic data capture system. All data will be entered into the eCRF by the site staff. These data will then be source-data verified and reviewed by the study monitor (or Clinical Research Associate) before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and, once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked and the data released for summary and analysis. All summary and analysis of the data will be performed using SAS® version 9.3 and/or WinNonLin Pro (Version 6.3 Phoenix™, Pharsight®), or later.

9.2 Study Monitoring

Study monitors will be responsible for the monitoring of the study.

The study monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review the eCRF(s), patient case notes, administrative documentation, including the Investigator Site File, and to perform drug accountability will be performed throughout the study at appropriate intervals.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the Study Monitor, monitoring visits will be confirmed in advance of planned visits.

9.3 Clinical Study Audit

The Sponsor, Sponsor representative, or external regulatory agency may at any time during or after completion of the study conduct a GCP audit at any trial site. Prior notice will be given to each site selected for audit in advance of a planned audit.

9.4 Clinical Study Report

The results of the study will be presented in an integrated Clinical Study Report according to ICH guidelines.

9.5 Data Retention and Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, a disc containing all eCRF data (including the full audit trail and all data queries), signed informed consent forms, and records for the receipt and disposition of study medications, for a specified period required by ICH GCP, or longer if required by local or regulatory authorities.

US Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

European laws require that the Investigator maintain all study records (excluding the patients' medical files) for at least 15 years after completion or discontinuation of the trial, or for at least two years after the granting of the last marketing authorization in the European Community (EC) and where there are no pending or contemplated marketing applications in the EC, or for at least two years after the formal discontinuation of clinical development of the investigational product.

During the study, the Investigator must make study data accessible to the study monitor(s), the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IEC/IRBs and regulatory agencies. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

9.6 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (required in the US; in the EU, if applicable) and a financial disclosure statement (required in the US; in the EU, if applicable). Sub-investigators may also be required to provide a current curriculum vitae and a financial disclosure statement according to the regulations of the countries involved.

9.7 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC (Section 10). The exception to this is where modifications are necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (e.g. change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10 ETHICS REVIEW AND INFORMED CONSENT AND COMPETENT REGULATORY AUTHORITY APPROVAL

10.1 Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IEC/IRB, and the US Code of Federal Regulations, Title 21 CFR Part 50.

10.2 Institutional Review Board or Independent Ethics Committee Approval and Competent Regulatory Authority Approvals

The final study protocol and patient informed consent form will be approved by the appropriate IEC/IRB for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the trial will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant IEC/IRBs and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect patient safety, which will be implemented immediately.

If an amendment substantially alters the trial design, increases the potential risk to the patients, affects the treatment of the patient, or might otherwise influence the willingness of the patient to participate in the trial, then the information sheet must be revised and submitted to the relevant IEC/IRB and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing trial procedures and is affected by the amendment, then the patient must be asked to consent again using the new information sheet.

10.3 Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All patients will be informed that participation is voluntary and that they can cease their study treatment(s) and/or their further participation to any further study assessments at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

Patients will be provided with two consent forms prior to the commencement of any procedures or investigations:

i. The Main Consent to participate in the study will include information about the patient's disease, alternative treatment options, the study treatments and their duration, study design and study assessments and procedures, risks, side effects and potential benefits of participation. This consent will include:
    a. Consent to provide sufficient tumor tissue to enable Axl kinase and PD-L1 expression measurement by IHC, and an explanation that this includes the provision of a newly acquired tumor tissue sample.
    b. If possible, the electronic storage of all radiological and non-radiological scans at site for future reference (e.g. medical case studies, publications and training).

c. Information regarding the expected (maximum) blood volume to be provided.
d. Information that treatment with checkpoint inhibitors, such as pembrolizumab, is occasionally associated with worsening of disease before clinical improvement is observed. Therefore, their treatment may continue if their doctor suspects that the patient is benefiting from the treatment.
e. Information that treatment with checkpoint inhibitors, such as pembrolizumab, and treatment with BGB324 are associated with side effects and that the patient must inform the doctor of any side effects, even if the patient does not think they are important.
f. An explanation that patients will continue to have 12 weekly follow-up visits (or in some cases, a telephone call) to assess their disease and/or well-being after the completion of their study treatments. Follow-up visits or telephone contact will continue until the end of the study.
g. Information to explain that on-study blood samples will be collected for the purpose of assessing biomarkers of Axl signaling and inhibition.

ii. A separate Optional Consent for the provision of a baseline archival tumor tissue sample for the purpose of exploratory biomarker analysis will be presented to the patient.

During the trial, patients may be offered a further consent to provide an optional newly acquired tumor tissue sample for exploratory biomarker assessment.

The patient must give consent (the Main Consent form) to participate prior to enrolment in the trial. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team (e.g. Sub-Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Site Study File. By giving signed consent, the patient will confirm that his or her participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form(s) will be kept by the Investigator. Prior to participation in the trial, the patient should receive a copy of the signed and dated written informed consent form(s).

The consent forms must include all elements required by law, local regulations, GCP and ICH guidelines including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the patient's medical records. This gives permission to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the trial.

10.4 Patient Participation Card

A study participation card will be provided to each patient on the trial. The card will indicate that he or she is participating in a clinical trial and give the name and contact details of the Sponsor and the Investigator/study site. The patient will be asked to retain this card while participating in the trial and show it to any other medical practitioners consulted during this time. Patients will be advised to contact the Investigator/study site if there are any questions.

A sample patient participation card is shown in Figure 6 below:

Figure 6: Sample Patient Participation Card

Dear Patient, ***Please inform any physician you are going to visit during the course of the study that you are participating in a clinical trial by presenting this contact card.*** ***Please carry this card with you at all times until the end of the study.*** ***INSERT NAME*** is participating in an open-label trial of an experimental drug called BGB324 in combination with pembrolizumab in patients with triple negative breast cancer. **Subject No.:** (optional)	**Study Contact Card** **Clinical Trial BGBC007/ MK-3475 PN 530** **Eudract Number: 2016-003608-30** ***Dear Doctor,*** ***In the case that additional medications must be prescribed to this patient, or you need more information about the clinical trial they are participating in, or you need to notify the study physician about the patient's worsening condition, please contact:*** **INSERT NAME, ADDRESS & CONTACT NO.**

10.5 Insurance

Appropriate insurance for this clinical trial will be arranged by the Sponsor in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the TMF and in the Investigator Site File.

10.6 Patient Privacy

Any party with direct access to patient records or any material which identifies the patient must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the patients' identities and Sponsor's proprietary information.

In order to maintain patient confidentiality, all CRFs, study reports and communications relating to the study will only identify patients by their assigned study number; patients should not be identified by name. Depending on the countries involved in the clinical trial, use of patient initials, and full date of birth may be prohibited.

11 PUBLICATION POLICY

The original eCRFs and all data generated during the clinical study using the given protocol will become the property of the Sponsor.

Any proposed publication or presentation (including a manuscript, abstract, or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review at least 1 month prior to submission. No single center or groups of centers may publish individually. Publications arising from this clinical study will include all Investigators as authors. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. Sponsor may delay such submission by a maximum of 90 (ninety) days if it reasonably believes that publication of results may compromise its intellectual property rights or else insist that such information or data are removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

The Sponsor may announce quality assured summary data in order to comply with Financial Regulatory Authorities, while ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

APPENDIX A: Easter Cooperative Oncology Group Performance Status

Grade	ECOG Performance status[24]
0	Fully active. Able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Creatinine Clearance Algorithm

Creatinine clearance should be calculated using the Cockroft-Gault Formula[25], which is given below:

US calculation formula:

$$\textbf{CrCl} = \frac{\textbf{(140 - Age) x Mass (kilograms) x (0.85 } \textit{\textbf{if Female}}\textbf{)}}{\textbf{72 x serum Creatinine (mg/dL)}}$$

European calculation formula:

$$\textbf{Males:} \quad \frac{\textbf{1.25 x (140 – age) x weight (kg)}}{\textbf{Serum creatinine (µmol/l)}}$$

$$\textbf{Females:} \quad \frac{\textbf{1.05 x (140 – age) x weight (kg)}}{\textbf{Serum creatinine (µmol/l)}}$$

APPENDIX C: The New York Heart Association (NYHA) Functional Classification in a Patient with Heart Disease

Overview: The NYHA developed a functional classification for patients with heart disease.

Patients: Heart disease must be present.

Parameters:

- Limitations on physical activity
- Symptoms (undue fatigue palpitations dyspnoea and/or anginal pain) with ordinary physical activity
- Status at rest

Limitations on Physical Activity	Symptoms with Ordinary Physical Activity	Status at Rest	Class
none	none	comfortable	I
slight	symptomatic with ordinary activities	comfortable	II
marked	symptomatic at less than ordinary levels of activity	comfortable	III
unable to perform any activity	discomfort with any activity	symptomatic at rest	IV

From The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. (1994). (9th ed.). Boston: Little, Brown & Co. 253 – 256

APPENDIX D: Drugs Associated with Torsades de Pointes

See example list below. The following website for an updated list of drugs that may cause Torsades de Pointes www.AZCERT.org

Generic Name	Brand Name
Amiodarone	Coradone/Pacerone
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox
Astemizole	Hismanal
Azithromycin	Zithromax®, Zmax®
Bepridil	Vascor
Chlorquine	Arelan
Chlorpromazine	Thorazine
Cisapride	Propulsid
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Dronedarone	Multaq®
Droperidol	Inapsine
Erythromycin	Erythrocin/E.E.S.
Escitalopram	Cipralex®, Lexapro®
Flecainide	Tambocor®, Almarytm®
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Covert
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Methadose/Dolophine
Moxifloxacin	Avelox
Ondansetron	Zofran®, Anset®
Petamidine	NebuPent/Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl/Procan
Quinidine	Cardioquin/Quinaglute
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace
Sparfloxacin	Zagam
Sulpiride	Dogmatil®, Dolmatil®
Terfenadine	Seldane

Thioridazine	Mellaril
Vandetanib	Zactima

APPENDIX E: Local Laboratory Parameters

Clinical Chemistry	***Hematology, including Coagulation***
Calcium	Red cell count, mean corpuscular volume
Total protein	Hemaglobin, free hemaglobin
Albumin	Absolute reticulocyte count
Total bilirubin	Platelet count
Alanine transaminase (ALT, SGPT)	White blood cells
Aspartate transaminase (AST, SGOT)	Leucocyte differential count (% & absolute)
Lactate dehydrogenase (LDH)	International normalized ratio or prothrombin time
Alkaline phosphatase	Activated partial thromboplastin time
Glucose (random)	***Urinalysis***
Sodium	Glucose
Potassium	Protein
Bicarbonate	Bilirubin
Chloride	Ketones
Magnesium	Blood
Urea = Blood urea nitrogen	pH
Creatinine	Specific gravity
Phosphate	Microscopic examination when indicated
Amylase	FSH (female menopausal patients; at Screening
TSH, Free T4, T3, Free T3	HCG (female pre-menopausal patients; at Screening)

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