Statistical Analysis Plan

Sponsor Name:	**BerGenBio ASA**
Protocol Number and Title:	**BGBC007** **Merck & Co: MK-3475 PN-530** **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)**
Protocol Version and Date:	**Final Version 1.0, dated 02 Nov 2016** **Version 2.0, dated 13 Apr 2017** **Version 3.0, dated 22 May 2017** **Version 4.0, dated 13 Jun 2017**
INC Research Project Code:	**1007823**
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SAP Version:	**Final Version 1.0**
SAP Version Date:	**17 November 2017**

Revision History

Version #	**Date** (dd-mmm-yyyy)	**Document Owner**	**Revision Summary**
Draft Version 0.1	24 Aug 2017	[redacted]	Initial Release Version –draft version 01
Draft Version 0.2	17 Nov 2017	[redacted]	Updated draft Version 02
Final Version 1.0	14 Dec 2017	[redacted]	Final Version 1.0

I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
CI	Confidence Interval
CM(s)	Concomitant medication(s)
C_{max}	Maximum concentration achieved
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DCR	Disease Control Rate
DoR	Duration of Response
DRC	Data Review Committee
DY	Relative Day
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
Gmean	Geometric Mean
IV	Intravenous(ly)
K-M	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LPLV	Last patient, last visit
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MUGA	MULTI Gated Acquisition Scan
N	Number
N/A	Not Applicable

Abbreviation	Description
NA	Not Applicable
NC	Not Calculable
NCI	National Cancer Institute
NQ	Not Quantifiable
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
StD	Standard Deviation
$t_{1/2}$	Elimination half-life
TEAE	Treatment Emergent Adverse Event
TLF(s)	Table(s), Listing(s) and Figure(s)
t_{max}	Time of maximum concentration
TN-IBC	Triple Negative Breast Cancer
TNBC	Triple Negative Inflammatory Breast Cancer
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

INC Research will perform the overall safety and efficacy statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs).

Pharmacokinetic (PK) analyses will be performed by Charlie Brindley (labs based in Scotland). Pharmacokinetic parameters will be estimated for each subject using a fully validated version of WinNonlin Pro (Version 6.3 PhoenixTM, Pharsight®), or later version as appropriate and the PK TLF outputs will be produced by INC Research.

2.2. TIMINGS OF ANALYSES

2.2.1. 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 subjects.

A Data Review Committee (DRC), consisting of Principal Investigators, the Sponsor's (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. 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.

2.2.2. End of Stage 1 – Efficacy Analysis

The DRC will meet to review the overall risk/benefit profile of the combination, together with the ORR after 28 subjects have had the potential for at least 24 weeks of follow-up. 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 subjects. Recruitment to the study will be halted whilst the Stage 1 interim analysis is conducted. Recruitment will recommence if the decision is made to continue to the maximum of 56 evaluable

subjects, which is when the final analysis will be performed. A full analysis will be performed at the end of stage 1.

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.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary 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 unresectable or metastatic TNBC or TN-IBC.

3.2. SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To assess the safety of BGB324 and Pembrolizumab when given in combination in patients with previously treated locally advanced and unresectable or metastatic TNBC or TN-IBC.
- 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.

3.3. EXPLORATORY OBJECTIVES

The exploratory objective of this study is:

- To assess relevant biomarkers

Note:
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 of the protocol.

However, results from other biomarkers (for example, for the assessment of Axl signaling and inhibition) might 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 of the protocol. INC Research will receive the biomarker results and merge with patient demographic and other baseline and outcome data, and produce a separate analysis plan and report (addendum to the CSR) for biomarker analysis. All samples will be destroyed within 5 years of the last subject being entered to Stage 1.

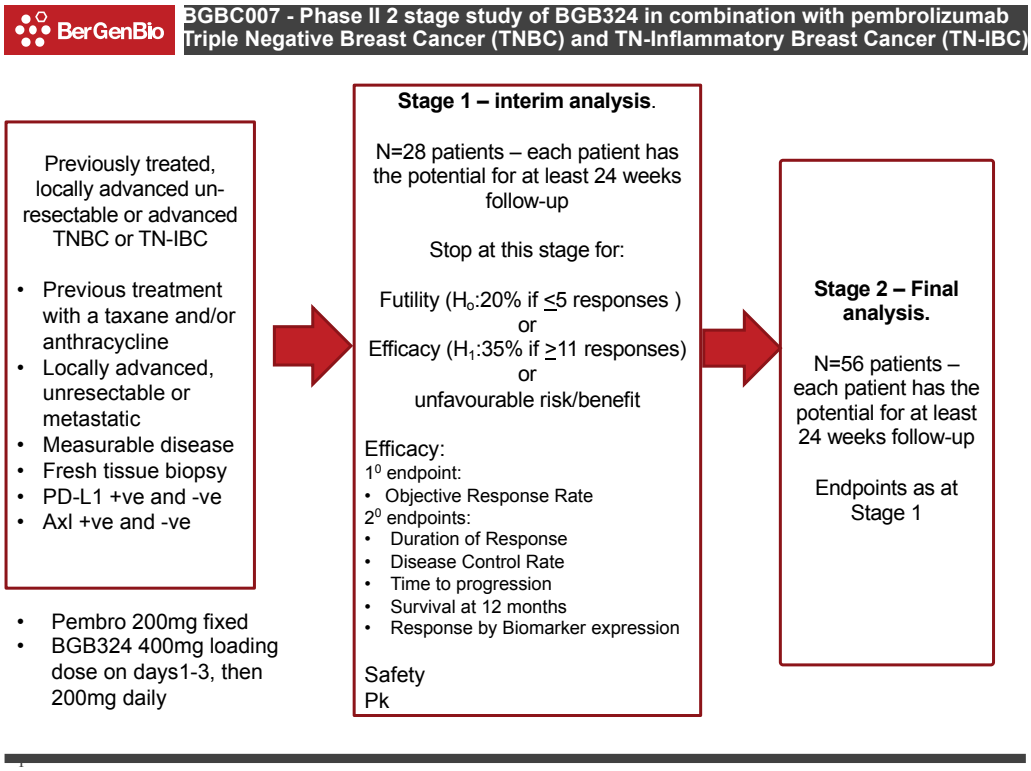
3.4. BRIEF DESCRIPTION OF STUDY

This is an open-label, multi-center, single arm, phase II study to assess the anti-tumor activity and safety of BGB324 when given 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 DRC will conduct a review of the safety data from the first 6 subjects who have had the potential to be followed for at least 6 weeks (minimum 2 cycles), and again when a further 6 subjects (12 subjects 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 utilise 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 subjects are evaluable for Objective Response Rate (ORR). If 5 or fewer responses are observed in up to 28 subjects, the trial will be terminated in favor of the null for futility. If 11or more responses are observed, then the trial will be stopped in favor of the alternative for demonstration of activity. Where 6 to 10 subjects have an observed response at the interim analysis, up to a further 28subjects may be evaluated, for a total of 56 subjects (see Section 8.1 of the protocol), taking the overall risk: benefit of the combination into consideration.

Recruitment to the study will be halted after 28 evaluable subjects 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 subjects. If a total of 17 or more responses are seen in 56 patients, then the null will have been rejected in favour of the alternative; otherwise the null will not have been rejected.

The following figure (Figure 1) summarizes the study design in a form of a diagram.

Figure 1: Schematic Diagram of the Study Design



3.5. SUBJECT SELECTION

Adult patients with pre-treated, advanced or metastatic TNBC will be enrolled in the study.

3.5.1. Inclusion Criteria

The inclusion criteria are defined in the protocol Section 3.1.

3.5.2. Exclusion Criteria

The exclusion criteria are defined in the protocol Section 3.2.

3.6. DETERMINATION OF SAMPLE SIZE

Up to 56 evaluable subjects will be enrolled in this study. Approximately 7564 patients will be screened in order to identify up to 5648 subjects who meet all of the inclusion

and exclusion criteria and who are evaluable for response. This assumes a 25% screen failure rate, given the need for subjects to provide a fresh tissue biopsy sample.

The study will employ a *k*-stage single arm design, an approach derived from basic statistical theory[2]. If p denotes the true tumor response rate with drug, the null and alternative hypotheses to be assessed in this trial are:

$$H_0 : RR=p_0 \text{ vs } H_1 : RR=p_1 \ (p_0 < p_1), \text{ with } p_0=0.20 \text{ and } p_1=0.35$$

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 subjects 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 subjects (l) are assessed for response and a final analysis is performed on all (m+l) subjects. 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 subjects. If 5 or fewer responses are observed in these 28 subjects, 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 subjects may be evaluated, for a total of 56 subjects. If a total of 17 or more responses are seen in 56 subjects, 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 the probability of correctly stopping for futility at the interim is 50.2% and, under the alternative, the probability of correctly stopping for activity at the interim is 38.4%. Consequently, the expected sample size for the design is 42-44subjects.

3.7. TREATMENT ASSIGNMENT & BLINDING

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

3.8. ADMINISTRATION OF STUDY MEDICATION

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 Days 1, 2 and 3. From Day 4 onwards, subjects will receive a daily dose of 200 mg daily. If the DRC recommend dose level -1 for new subjects (after or during the safety run-in), the dose of BGB324 will reduce to a loading dose of 200mg on Days 1, 2 and 3 and to 100mg from Day 4 onwards.

A fixed dose of 200mg Pembrolizumab will be given by intravenous (IV) infusion over 30 minutes every 3 weeks in all subjects. The 3-weekly dosing 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 1.

Table 1: 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 subjects will be observed for 1 hour for infusion or other adverse events (AEs). BGB324 may then be administered.

3.8.1. Duration of Treatment

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 (see Section 66. of the protocol), 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).

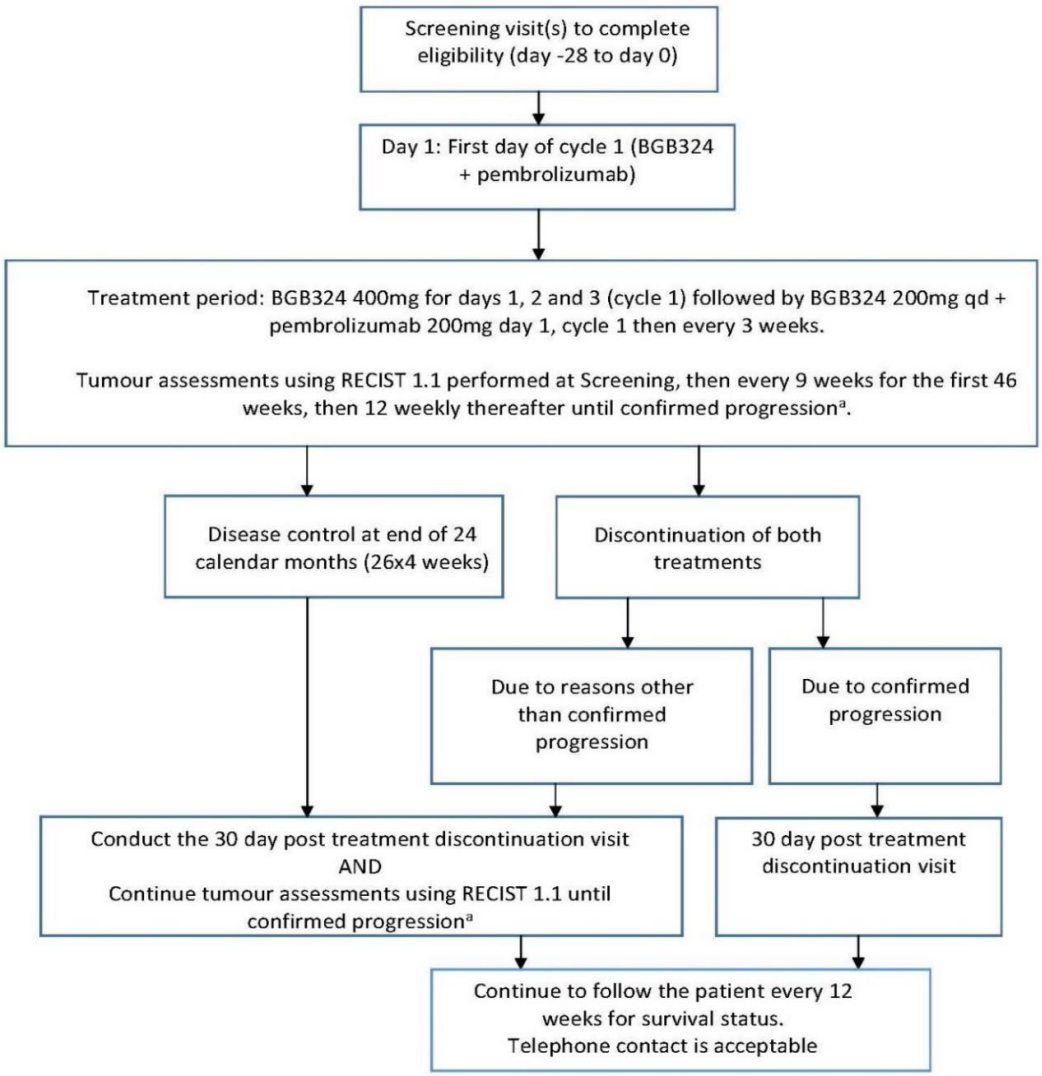
Otherwise, in the absence of progression, toxicity, or other reason for stopping treatment, Pembrolizumab in combination with BGB324 will be given until the end of cycle 35 (this cycle ends at approximately week 106, 24 months).

3.9. STUDY PROCEDURES AND FLOWCHART

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. Subjects must provide informed consent prior to commencing the study screening procedures. All subjects 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. Subjects 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 (+/- 3 days) after the subject has discontinued both study treatments. All subjects 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 (see Figure 2).

The study schedule will continue in keeping with the Study Assessment calendar. Subjects 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 relative to Day 1. 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 6.5.3 of the protocol for details on Pembrolizumab related toxicity dose interruption, including the duration of dose interruption.

Figure 2: Study 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.

Please refer to Schedule of Study Assessments (Table 3 and Table 4) for full details of all study assessments. Table 2 summarizes the timing of Pembrolizumab administration up to Cycle 35 (approximately 24 months of treatment) in relation to the timing of

disease assessment. Table 3 summarizes the schedule of assessments in Year 1 and Table 4 summarizes the schedule of assessments in Year 2. Assessments requiring specific timing relative to the BGB324 or Pembrolizumab dose are described in the footnotes to Schedule of Study Assessments – Table 3 and Table 4.

Subjects 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 subjects 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.

Subjects who withdraw from either or both study treatments prior to disease progression will continue to have tumor imaging assessments on study every 12 weeks until disease progression is documented (and confirmed, if necessary). The date of disease progression will be captured.

Subjects will continue to have their survival status checked every 12 weeks until either the subject dies or the study ends.

Table 2: Pembrolizumab 3-Weekly Schedule and Disease Assessment Timings

Year 1, First 6 months*									
Week:	**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:	**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:	**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:	**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 (+/- 7 days):	X				X				X

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

Table 3: 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 4: 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 drug. 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 of the protocol). 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).

4. ENDPOINTS

4.1. PRIMARY ENDPOINT

The primary endpoint for this study is the Objective Response Rate (complete response and partial response).

4.2. SECONDARY ENDPOINTS

The secondary endpoints of this study will consist of:

- The number and frequency of adverse events;
- Safety laboratory parameters;
- Vital signs;
- 12-Lead Electrocardiograms (ECGs);
- Disease Control Rate (DCR);
- Duration of Response (DoR);
- Progression-Free Survival (PFS);
- 12-month Overall Survival (OS);
- Pharmacokinetic parameters including C_{max}, AUC, $t_{1/2}$.

4.3. EXPLORATORY ENDPOINTS

The exploratory endpoints of this study will consist of:

- PD-L1 and Axl expression in patients with TNBC and TN-IBC;
- Any correlation or association between expression level of PD-L1 and Axl;
- Anti-tumor outcomes, such as ORR;
- Assessment of relevant biomarkers in tumor and blood which support immune modulation and Axl signaling.

5. ANALYSIS SETS

5.1. SCREENED SET

The Screened Set will include all subjects who are enrolled in the study or are screening failures. The Screened Set will be used for the listing and summaries of subject disposition and for the listing of Adverse Events and protocol deviations.

5.2. SAFETY SET

The Safety Set will include all subjects who are enrolled in the study and who have received at least one dose of study product (BGB324 and/or Pembrolizumab). The Safety Set will be used for all analyses of safety endpoints and for the presentation of subjects in all subject listings, with the exception of subject disposition, protocol deviations, efficacy and AE listings.

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

5.3. EVALUABLE ANALYSIS SET

The Evaluable analysis set will include all evaluable subjects; subjects that have received at least one combination dose of Pembrolizumab and BGB324 and who have measurable disease at entry, as determined by the Investigator Site assessment. The Evaluable analysis set will be used for summarizing and listing the efficacy objectives.

5.4. PROTOCOL DEVIATIONS

Protocol deviations will be addressed by monitoring on an ongoing basis. All protocol deviations are to be recorded in RAVE (Table 5) with the indication of whether they are major or minor as determined by the Study Management Team, in cooperation with Data Management, Medical Monitoring, and the Sponsor.

All protocol deviations will be listed only for all subjects in the Screened Set, including their assignment of minor or major, the date the deviation occurred and the action taken.

Table 5: List of protocol deviations that are recorded in Rave

Protocol Deviation Category	Important	Non-Important
Inclusion/Exclusion Criteria: I/E not met	x	

Protocol Deviation Category	Important	Non-Important
Informed Consent: ICF not signed or signed late	x	
Informed Consent: ICF used was not current approved version	x	
Informed Consent: Other	x	
Randomization: Treated and not Enrolled	x	
Randomization: Multiple Enrolments of the same patient	x	
Randomization: Other	x	
Investigation Product/Dosing: IP Storage issues, IP provided to subject	x	
Investigation Product/Dosing: IP Storage issues, IP NOT provided to subject		x
Investigation Product/Dosing: IP Dosing – patient did not receive dose per protocol	x	
Investigation Product/Dosing: IP Dosing – site did not adhere to dose reduction guidelines	x	
Investigation Product/Dosing: other	x	
Study Procedures: Prohibited Concomitant Treatment		x
Study Procedures: PK samples not collected or not collected per protocol	x	
Study Procedures: Biopsy not collected as per protocol/lab manual	x	
Study Procedures: SAE or ECI reported late	x	
Study Procedures: Visit not performed within visit window		x
Study Procedures: ECGs not performed	x	
Study Procedure: Other Procedure not performed		x
Study Procedure: Site Staff Authorization, Delegation, Training		x
Study Procedures: Patient Met withdrawal criteria but not withdrawn	x	

Protocol Deviation Category	Important	Non-Important
Study Procedures: Imaging not performed per protocol, including the scheduled CT scans for PD confirmation	x	
Study Procedure: Other		x

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

This section describes analytical analysis issues that relate to all or some of the analytic analysis sections that follow. It describes general guidelines for analysis as well as the following items:

- SAS version 9.3 or higher will be used.
- INC Research will be responsible for reporting the demographic, safety and efficacy data, including the listings and tables of PK data. However, INC Research is not responsible for the derivation of the PK parameters.
- Unless otherwise specified, summaries will be presented by dose level (if needed based on the DRC recommendation) and overall.
- The total number of subjects in the treatment group will be used as the denominator for percentage calculations, unless stated otherwise in the table shell.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.
- All subjects who provide informed consent will be accounted for in this study.
- In general, the listings will be sorted by subject number and assessment date (and time), if applicable.
- Multiple assessments at a given time point (planned, repeat, and unscheduled) will not be included in summary tables unless specified otherwise, but will be included in the listings. For example if there are multiple laboratory results at a given visit, the closest value to the scheduled visit date will be used, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the subject that contributed to the summary table, wherever feasible.
- See Section 15 for INC standard programming conventions.

6.2. KEY DEFINITIONS

Study Day is the day relative to the date of first dose of study drug, where Day -1 is the day before the first dose of study drug and Day 1 is the day of study drug. Note that 'study drug' refers to BGB324 and/or Pembrolizumab.

The first dose date is defined as the first non-missing date where a non-zero dose of study drug was recorded.

The last dose date is defined as the last non-missing date where a non-zero dose of study drug was recorded. For subjects ongoing at time of analysis, last dose date will be considered the date of the most recent study visit in the database for that subject where a non-zero dose of study drug was recorded.

Unless otherwise specified, baseline is the last non-missing observation before the start of study drug, which is expected to be the on Day 1 of Cycle 1 (pre-dose) or Screening if the Day 1 data are not available.

For interim analysis if a subject is ongoing in the study at the time of data cut off then the day of the data cut off will be used as the last dose date.

6.3. MISSING DATA

Missing data (other than presented here) will not be imputed. Analyses will be performed considering all data observed for the respective analysis sets.

For the purpose of assigning adverse events (AEs) and concomitant medications, the followings rules will be applied for partial start and end dates:

Partial/missing start date:

- Should the day be missing, impute the first day of the given month unless the month and year are the same as the month and year of the first dose of study drug, then impute the first dose date.
- Should the day and month be missing, impute the date as 1st January unless the year is the same as the year of the first dose of study drug, then impute the first dose date.
- Should the full date be missing, impute the first dose date unless the end date suggests the event/medication could have started prior to this, in which case impute the 1st January of the same year as the end date.
- When imputing a start date, ensure that the newly imputed date is sensible i.e. prior to the end date of the AE or medication.

Partial/missing end date:

- Should the day be missing, impute the last day of the given month unless the month and year are the same as the month and year of the last dose of study drug, then impute the last dose date.

- Should the day and month be missing, impute the date as 31st December unless the year is the same as the year of the last dose of study drug, then impute the last dose date.

- Should the full date be missing, the ongoing status of the AE/medication and the start date in relation to the study drug should first be considered. If it is unknown whether or not the AE/medication is ongoing, assume that the AE is still present/medication is still being taken (i.e. do not impute a date). If, however, the AE/medication has stopped and the start date is prior to the first dose date, then impute the first dose date, unless it started on or after the first dose date, then impute a date that is after the first dose date.

In case date of diagnosis is partial missing, please impute:
- Should the day be missing, impute the first day of the given month.
- Should the day and month be missing, impute the date as 1st January.

6.4. VISIT WINDOWS

There are no plans to derive visit windows, visits will be used in the analyses as reported on the eCRF.

6.5. POOLING OF CENTERS

The data from the individual centres will be pooled. The analyses will be based on the pooled data.

6.6. SUBGROUPS

No subgroup analysis is planned.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition at the end of Screening will be summarized for all subjects in the Screened Set. The summary table will show the frequency and percentage of subjects who either completed the Screening period and entered the treatment phase or failed Screening, along with the primary reasons for failure and whether or not the subject has measurable disease.

Subject disposition at the end of treatment and the end of study will also be summarized in the same table for all subjects in the Safety Set, with the frequency and percentage of subjects who completed both or either one of the two treatments (BGB324 and/or Pembrolizumab) and who discontinued early, along with the primary reasons for discontinuation of study treatment, and the frequency and percentage of subjects who terminated the study early, along with the primary reasons for termination, respectively.

The number and percentage of subjects included, and reasons for exclusion, from each of the analysis sets will also be tabulated.

Informed consent and eligibility criteria met/not met will be listed only.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All demographic and baseline characteristic data will be summarized for all subjects in the Safety Set.

Gender and child-bearing potential (female subjects only), ethnicity and race will be summarized by the number and percentage of subjects in each category.

Age (years), height (cm) and weight (kg) captured at Screening will be summarized as continuous variables.

Unless otherwise stated, percentages will be calculated out of the number of subjects in the Safety Set.

All demography data will be listed.

7.3. MEDICAL / SURGICAL HISTORY

Descriptions of medical/surgical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or later. Medical/surgical history, as recorded at Screening, will be summarized for the Safety Set by the number and percent of subjects within each system organ class (SOC) and preferred term (PT).

Conditions that are reported more than once for a given SOC and PT will be counted only once per subject on the PT level for each SOC. Medical/surgical history will be sorted by descending overall frequency, by SOC and PT in the summary table.

Medical/surgical history shall also be listed for all subjects in the Safety Set.

Medical history data listings will be sorted by subject number, onset date, SOC, and PT.

7.4. OTHER BASELINE CHARACTERISTICS

7.4.1. Cancer Diagnosis

Cancer diagnosis, as recorded at Screening, shall be summarised by the number and percentage of subjects within each category for the following:

- Current stage of disease (I-IV);
- If the subjects have any known mutations (yes/no);
- Mutation type (EGFR, ALK, Kras and other).

The time from initial diagnosis and time from advanced or metastatic disease to informed consent (years) shall be summarized as continuous variables using descriptive statistics where:

Time from Initial Diagnosis to Informed Consent (years) =	(Date of Informed Consent – Date of Initial Diagnosis + 1)/365.25
Time from Advanced or Metastatic Disease to Informed Consent (years) =	(Date of Informed Consent – Date of Initial Diagnosis + 1)/365.25

All cancer diagnosis data shall also be listed for all subjects in the Safety Set.

7.5. MEDICATION

Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD). Medications will be classified as concomitant or prior, as defined in the Sections 7.5.1 and 7.5.2 respectively, and summarized by ATC class (level 2) and sub-class (PT) for all subjects in the Safety Set.

Any concomitant medication will be recorded at each visit, including the medication name, indication, dose, unit, route of administration, frequency and medication start and end dates.

Prior and concomitant medications will be summarized separately. All prior and concomitant medications will also be listed including the derived study day (for both start and stop dates), with a flag identifying prior medications.

The summary tables will show the frequency and percentage of subjects with at least one usage of medication on the sub-class level within each ATC class, sorted alphabetically.

Percentages will be calculated out of the number of subjects in the Safety Set.

7.5.1. Prior Medication

Prior medications are those medications that were stopped prior to first study drug administration.

7.5.2. Concomitant Medication

Concomitant medications (CMs) are medications that are ongoing at or began after the start of study drug. Medications without an onset date will be defined as concomitant, except if an incomplete date (e.g. month and year) clearly indicates that the medication was started prior to the start of study drug or if the medication stop-date indicates that the medication was started and stopped prior to the start of study drug. Partial medication dates will be imputed as detailed in Section 6.3.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for Serious Adverse Events (SAEs) and Events of Clinical Interest (ECIs).

Sections 6.7 and 6.8 of the protocol detail permitted and restricted concomitant medications and acceptable concomitant medications, respectively, along with prohibited concomitant medications whilst receiving Pembrolizumab in Section 6.9 of the protocol.

7.6. OTHER THERAPIES

7.6.1. Prior Radiotherapy

Summary tables for prior radiotherapy shall display the number and percentage of subjects with at least one prior radiotherapy, as well as for each site and administration setting recorded.

The time since the last dose (years) shall be summarized as a continuous variable using descriptive statistics where:

Time Since Last Dose (years) = (Date of Informed Consent – Date of Last Dose + 1)/365.25

All prior radiotherapy data shall also be listed for all subjects in the Safety Set.

7.6.2. Prior Anticancer Therapy for Study Disease

Prior anticancer therapy for the study disease shall be summarized for all subjects in the Safety Set, considering the number of regimens through the number and percentage of subjects for each category (categorised as 0, 1, 2, 3, 4, 5 and >5) and using descriptive statistics, as well as the number and percentage of subjects with immunomodulatory agents (yes/no).

All prior anticancer therapy for the study disease data, including regimen number, agent, immunomodulatory agent, route, setting, start and stop dates, best response and progression date as recorded at Screening shall be also listed.

8. EFFICACY

The efficacy analysis will be performed using the Evaluable analysis set.

The following efficacy endpoints will be summarized by time-point where disease assessments are performed, and analysed for both the interim and final analyses:

- Objective Response Rate (ORR);
- Duration of Response (DoR);
- Disease Control Rate (DCR);
- Progression Free Survival (PFS);
- Overall Survival (OS).

Efficacy endpoints will be based on tumor imaging evaluations performed by RECIST 1.1.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

Each subject will be assigned one of the following categories for modified RECIST response: CR (Complete response), PR (Partial response), SD (Stable disease), PD (Progression of disease), NE (Not evaluable). The applicable overall response category for each visit that includes tumor assessment will be recorded in the eCRF.

The primary efficacy endpoint is the Objective Response Rate (ORR), defined as the percentage of evaluable subjects who have at least one (confirmed) overall response of complete response (CR) or partial response (PR). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. A subject who has discontinued both treatments, and subsequently responds having received a subsequent anti-cancer treatment will be excluded from the subset of responding subjects; however these subjects are evaluable and will be included in the denominator. ORR will be presented by percentage rates and 90% CIs, where the 90% CI will be calculated assuming an exact binomial distribution.

All response assessments will be listed. A summary of overall response at each visit will also be included.

A sensitivity ORR analysis, defined as the percentage of evaluable subjects who have at least one overall response (irrespective of confirmation) of complete response (CR) or partial response (PR) will be conducted.

Note: 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.

The target lesions, non-target lesions, new lesions, and overall tumor response data recorded will be listed. The best overall response will also be summarized. A patient will be counted only once and the order from best to worse is CR>PR>SD>PD>NE (note NE = Not Evaluable). The sum of the longest diameters, the change from baseline in sum of diameters as well as the percent change from baseline will be also listed. Evaluations at Screening will serve as baseline values.

Additionally, a waterfall plot for RECIST best percentage change from baseline in the sum of target lesion longest diameters will be provided. The Y axis will be percent change from baseline and subject number on the X axis. A positive result indicates an increase in tumor volume from baseline; a negative result indicates a decrease (shrinkage).

Best percent change from baseline (%) in the target lesion=

([the minimum sum of the longest diameters at all post-baseline measurement time points – the sum of the longest diameters at baseline] / [the sum of the longest diameters at baseline]) x 100.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

8.2.1. Duration of Response

The Duration of Response (DoR) will only be calculated for subjects that have an objective response. The DoR is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression; the end of response should coincide with the date of progression or death from any cause. Subjects who continue to respond at the date of data cut-off (last subject, last visit) will be censored at their last clinical evaluation. Subjects who are lost to follow-up will be censored at their last clinical evaluation.

Duration of Response will be calculated for all subjects that experience documented CR or PR during the study in weeks as follows:

Duration of Response (weeks) = ([Date of Progression/Death/Censoring – Date of First Recorded CR or PR] + 1)/7

The Duration of Response will be presented as a swimmer plot with Duration of Response on the Y axis and patient number on the X axis. The swimmer plot will present all subject time-to-event data such as Complete Response Start, Partial Response Start, Stable Disease, time of progression or time of ongoing response at last visit, time of

treatment stop, Not Evaluable or Death.

The Duration of Response from onset of response will be analysed for all subjects achieving objective response during the study using a Kaplan-Meier (K-M) survival analysis. The K-M estimate of the median duration (with 95% CIs) of response and the 25th and 75th percentiles will be presented. A Kaplan Meier plot of the duration of response will also be presented.

8.2.2. Disease Control Rate

Disease Control Rate (DCR) is defined as the percentage of subjects with a 'Complete Response', 'Partial Response', or 'Stable Disease (out of number evaluable). Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of DCR.

Disease control is determined by the overall lesion response collected on the eCRF. If any response of 'Complete Response', 'Partial Response', or 'Stable Disease' is obtained, then Disease Control = 'Yes' (even if a subject has a disease progression later). If only response of 'Progressive Disease' or 'Not evaluable for a response' is obtained, then Disease Control = 'No'. Subjects with missing overall lesion responses (but who do have a post first dose record for target lesion assessment) will be treated as Disease Control = 'No', i.e. they will be included in the denominator when calculating the percentage. DCR will be analysed by computing the estimate of disease control and the exact binomial 95% confidence intervals (CIs).

8.2.3. Progression Free Survival

Progression Free Survival (PFS) is defined as the duration from start of the treatment (Cycle 1 Day 1) until the date of disease progression (the date on which the confirmed progression is initially observed) or the date of death (regardless of cause of death), whichever is earlier. Subjects who have not progressed or died before the date of data cut-off (last subject, last visit) will be censored at their last clinical evaluation (last evaluable RECIST assessment). Subjects who are lost to follow-up will be censored at their last adequate assessment to be alive.

PFS (weeks) = ([Date of Progression/Death/Censoring – Date of First Dose] + 1)/7

PFS analyses will be performed using investigator lesion assessments (for RECIST v1.1 criteria) collected in the eCRF.

PFS will be analysed for all subjects in the evaluable analysis set using a K-M survival analysis. The number of events, percentiles for the PFS (25%, 50% (median and 95% CIs), and 75% percentiles), and the proportion of subjects who are progression-free at 12 months will be summarized. Kaplan Meier plots of the time to progression and death will also be presented.

A sensitivity summary of PFS using the first date that a progression is considered (irrespective of whether confirmed) will additionally be conducted.

8.2.4. Overall Survival

Overall survival (OS) is defined as the time from the first dose of study treatment until the date of death (from any cause and irrespective of any subsequent anti-cancer treatment given).

Subjects who remain known to be alive at the date of data cut-off (last subject, last visit) will be censored at their date last known to be alive. Subjects who are lost to follow-up will be censored at the point last known to be alive; however, if ≥2% of subjects is in this category, a sensitivity summary will be produced to illustrate the overall survival assuming the subject died at the date last known in the trial

OS (weeks) = ([Date of Death/Censoring – Date of First Dose] + 1)/7

Overall survival will be summarised by survival status. The number of events and estimates for the 25%, 50% (median and 95% CIs), and 75% percentiles for OS will be presented. The proportion of subjects who are surviving at 12 months will also be summarized. Kaplan Meier curves will be plotted.

Data collected at the survival follow-up visit (i.e. subject status (dead, alive, lost to follow up and previously documented disease progression)) will be listed.

9. ANALYSIS OF PHARMACOKINETICS

PK parameters will be estimated for each subject using a fully validated version of WinNonlin Pro (Version 6.3 PhoenixTM, Pharsight®), or later version as appropriate. The following parameters (Table 5) will be derived for BGB324, where appropriate, from the individual plasma concentration versus time profiles from all subjects.

Actual blood sampling times post dosing will be used in calculation of PK parameters. If actual sampling time is missing, nominal time may be used with sponsor approval. Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with the amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

Table 6: Pharmacokinetic parameters

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

The maximum plasma concentration (C_{max}), the time of maximum concentration (t_{max}) will be determined by inspection of the concentration-time profiles.

The area under the plasma concentration-time curve up to 24 hours ($AUC_{(0-24)}$) will be calculated using the linear up/ log down trapezoidal rule.

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).

The sections below will present the pharmacokinetic analysis in details.

9.1. PRESENTATION OF CONCENTRATION DATA

PK data will be summarised using the safety analysis subset. Plasma concentrations of BGB324 and metabolite will be summarised by nominal sample time.

Plasma concentrations and derived PK parameters will also be presented by the following summary statistics:

For $AUC_{(0-24)}$ and C_{max}:

- Number of observations

- Minimum
- Maximum
- Geometric mean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale
- CV, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale
- Standard deviation of geometric mean
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Median

For t_{max}:

- Number of observations
- Minimum
- Maximum
- Median

For $t_{½}$:

- Number of observation
- Arithmetic mean
- Standard deviation
- Median
- Minimum
- Maximum

Plasma concentrations below LLOQ will be reported as not quantifiable (NQ) with the LLOQ defined in the TFLs.

For calculation of summary statistics for plasma concentrations:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the gmean, CV, gmean ± standard deviation, arithmetic mean and standard deviation will be calculated by substituting the limit of quantification (LOQ) for values which are NQ.

- If more than 50%, but not all, of the concentrations are NQ, the gmean, CV, gmean ± standard deviation, arithmetic mean and standard deviation will be reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set as NQ.

- If all the concentrations are NQ, the gmean and arithmetic mean will be reported as NQ and the CV, gmean ± standard deviation, and standard deviation as NC.

The number of values above LLOQ will be reported for each time point along with the total number of collected values.

Three observations >LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values will be presented as a minimum and maximum with the other summary statistics as NC.

PK parameters will be presented according to the conventions listed in the table below.

Parameter	Reporting in Summary Tables	Listings
$AUC_{(0-24)}$	gmean/CV/gmeanSD/mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
C_{max}	gmean/CV/gmeanStD/mean/SD/med = 4 s.f. min/max = 3 s.f.	same s.f. as supplied from bioanalysis
$t_{1/2}$	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
t_{max}	med = 2 d.p. min/max = 2 d.p.	2 d.p.

N number included in summary table for all parameters as whole numbers.
d.p. decimal places
s.f. significant figures

The following figure will be produced:

- The geometric mean concentration (+/-standard deviation) versus time.

10. EXPLORATORY OBJECTIVES

10.1.1. 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 below.

The ORR will be explored as follows:

- By PD-L1 status (+ve or –ve), using a Chi square or Fishers Exact Test;
- By Axl status (+ve or –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, subjects 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 possible categories (<1%, 1-49% and ≥50%), the subject will be regarded as PD-L1 positive if their TPS is ≥1%.

A subject 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.

However, other biomarkers are exploratory and as such, the respective samples might not be available at the time of clinical database lock. A separate analysis plan and report for biomarker analysis will be written.

11. SAFETY

The Safety Set shall be used for all safety analyses. Safety will be assessed on the basis of AE reports, clinical laboratory data, vital signs measurements, ECOG performance status, 12-Lead Electrocardiogram (ECG) data and physical examination findings.

11.1. EXTENT OF EXPOSURE

The number of doses of BGB324 and Pembrolizumab by cycle and over the entire study period will be listed and summarised using descriptive statistics for all subjects in the Safety Set.

The extent of exposure to BGB324/Pembrolizumab will be examined by summarizing the total treatment duration using descriptive statistics.

The total treatment duration of exposure (total time on both BGB324 and Pembrolizumab, total time on BGB324 as monotherapy, total time on Pembrolizumab as monotherapy) (in weeks) is calculated as follows:

Total Treatment Duration (weeks) = [(date of last dose of BGB324 – date of first dose BGB324) + 1] /7

= [(date of last dose of Pembrolizumab – date of first dose Pembrolizumab) + 1] /7

= [(date of last dose of BGB324 (as monotherapy) – date of first dose BGB324 (as monotherapy) + 1] /7

= [(date of last dose of Pembrolizumab (as monotherapy) – date of first dose Pembrolizumab (as monotherapy) + 1] /7

Dose reductions (BGB324 only) and interruptions of BGB324 and Pembrolizumab shall be summarized by the number and percentage of subjects in each category. This data shall also be listed.

For the administration of Pembrolizumab, information on the batch number, infusion date and start and stop times, actual dose received (and units) and dosing action taken, along with reason for action, shall also be collected and listed only.

Similarly, for BGB324, information on the batch number, date and time of administration, dose administered and dosing action taken, along with reason for action, shall also be collected and listed only.

Details on the IP dispensation, including whether or not the subject shall receive Pembrolizumab/BGB324, the BGB324 dose to be administered, if the drug shall be dispensed to the subject and the kit/bottle number(s), shall also be collected and listed only.

11.2. TREATMENT COMPLIANCE

BGB324 compliance will be calculated as a percentage, with the total number of capsules taken overall (assuming any capsules not returned were taken by the patient) as the numerator and the expected total number of capsules taken as the denominator, i.e.

Percentage of Compliance (%) = (Total Capsules Taken / Expected Total Capsules Taken) x 100

The expected total number of capsules taken will be calculated by summing the number of days between study visits and multiplying by the number of capsules taken per day for the prescribed dose.

The percent compliance will be summarized with quantitative descriptive statistics and also with frequency and percentages of subjects with <80%, 80-<90%, and 90-100% compliance.

11.3. ADVERSE EVENTS

Adverse events (AEs) will be collected throughout the study, from time of consent until at least 30 days following cessation of treatment. Serious adverse events will be collected until 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whilst pregnancies will be reported for up to 120 days after cessation of treatment.

Subjects who signed a consent form and were screened but did not receive any treatment will be listed only if they reported an AE in the time after consent and before treatment allocation (see Section 7.1 of the Protocol).

Adverse events will be summarized by the System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary version 18.0 or later.

Treatment-emergent adverse events (TEAEs) are defined as any adverse events that commence on or after the first dose of study drug, or increased in severity if present prior to first dose, until exit from the study. Partial AE dates will be imputed (Section 6.3).

All AEs (including Serious Adverse Events [SAEs]) will be graded for severity using the National Cancer Institute (NCI) CTCAE version 4.03 (details of classifications are in Section 7.4.1 of the Protocol).

All AEs (including SAEs) will be assessed for the relationship of the AE to both Pembrolizumab and BGB324 study drug. The relationship of the study treatment to an AE will be determined by the Investigator and subsequently reviewed by the Medical Monitor. Relationships of 'definitely', 'probably' and 'possibly' are to be considered as related to study drug for the summary tables. Relationships of 'Not/unlikely related' are to be considered not related to study drug. If the relationship to study drug is missing for TEAEs then the relationship will be counted as related to both Pembrolizumab and BGB324 for the summary tables. Similarly, missing severity for TEAEs will be counted as Grade 3 ('severe'). Note that the original relationship, as recorded in the eCRF, shall be presented for data listings.

Selected non-serious and SAEs are also known as Events of Clinical Interest (ECI), and these will be identified on the CRF. Details of ECI are given in Section 7.4.3.2 of the Protocol.

The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects.

For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT level within the SOC level. For summaries by SOC, PT, and maximum intensity, a subject will be counted once at the highest grade for which the event occurred at the SOC level and the highest grade for each unique PT level within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following AE tables will be provided:

- An overall summary of the number and percentage of subjects reporting AEs, TEAEs, serious TEAEs, Events of Clinical Interest (ECI), TEAEs related to both study drugs separately, TEAEs of CTCAE grade 3 or higher, TEAEs of CTCAE grade 3 or higher and related to both study drugs, TEAEs leading to interruption of study drug (BGB324 and Pembrolizumab separately), TEAEs leading to discontinuation of study drug and fatal TEAEs;
- TEAEs overall and by system organ class (SOC) and preferred term (PT);
- TEAEs by maximum reported CTCAE grade, overall and by SOC and PT;
- TEAEs of CTCAE grade 3 or higher, overall and by SOC and PT;
- TEAEs by relationship to BGB324 overall and by SOC and PT;

- TEAEs by relationship to Pembrolizumab overall and by SOC and PT;
- TEAEs related to bothBGB324 and Pembrolizumab, overall and by SOC and PT;
- Events of Clinical Interest (ECI), overall and by SOC and PT;
- Events of Clinical Interest (ECI) related to both BGB324 and Pembrolizumab, overall and by SOC and PT;
- Serious TEAEs, overall and by SOC and PT;
- Serious TEAEs related to both BGB324 and Pembrolizumab, overall and by SOC and PT;
- TEAEs leading to interruption of BGB324, overall and by SOC and PT;
- TEAEs leading to interruption of Pembrolizumab, overall and by SOC and PT;
- TEAEs leading to interruption of both BGB324 and Pembrolizumab, overall and by SOC and PT;
- TEAEs leading to discontinuation of BGB324, overall and by SOC and PT;
- TEAEs leading to discontinuation of Pembrolizumab, overall and by SOC and PT;TEAEs with an outcome of death, overall and by SOC and PT.

With the exception of the overall summary AE table and the ECI summaries, only the TEAEs will be included in the summary tables; however, all AEs will be included in the listings. TEAEs will be flagged in the listings. Any AE occurring before the first dose of investigational product (i.e. before Cycle 1 Day 1) will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within the defined 30 day Follow-up period after the discontinuation of study drugs will be included in the AE summaries.

Additional listings will be provided for deaths, AEs with an outcome of death, SAEs, ECIs, AEs leading to the discontinuation of study drug and AEs leading to the interruption of study drug. TEAEs will be flagged in the listings.

11.4. LABORATORY EVALUATIONS

All subjects in the Safety Set will be included in the safety laboratory analysis.

The collection times of the blood and urine samples for safety assessment are recorded in the protocol.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

Clinical Chemistry:	Calcium, total protein, albumin, total bilirubin, alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), lactate hydrogenase (LDH), alkaline phosphatase, glucose (random), sodium, potassium, bicarbonate, chloride, magnesium, urea, creatinine, phosphate and amylase.
Hematology:	Including coagulation. Red cell count, mean corpuscular volume, hemoglobin, free hemoglobin, absolute reticulocyte count, platelet count, white blood cells, leucocyte differential count [% and absolute (neutrophils, lymphocytes, monocytes, eosinophils and basophils)], international normalized ratio or prothrombin time and activated partial thromboplastin time.
Urinalysis:	Glucose, protein, bilirubin, ketones, blood, pH, specific gravity, FSH (female menopausal subjects; at Screening) and HCG (female pre-menopausal subjects; at Screening).
Thyroid Function Test:	Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3) or Free Triiodothyronine (FT3) and Free thyroxine (FT4).

Laboratory data will be recorded at the following visits and time points:

- Hematology and Clinical Chemistry: at every visit, taken at a suitable time prior to the administration of study treatments.
- Coagulation (assessed from Hematology sample): Screening, Cycle 1 at Days 1, 8 and 15 only, then at each study cycle and at the Post-treatment visit.
- Urinalysis: Screening, Cycle 1 at Days 1, 8 and 15, Cycle 2 and at the Post-treatment visit.
- Thyroid Function Test (assessed from the Clinical Chemistry sample): Screening and then at every other cycle, starting at Cycle 3 (i.e., Cycle 3, Cycle 5, …, Cycle 35).
- Pregnancy and FSH Test: Screening (required within 3 days of Cycle 1 Day 1) and at each study cycle excluding the Post Treatment Visits for female subjects of reproductive potential.

Laboratory data (absolute values and absolute changes from baseline) will be summarized by visit for each parameter. Baseline is defined as the last non-missing pre-

dose value (pre both BGB324 and Pembrolizumab All summaries will be based on results in the International System of Units (SI units); conversion will be performed prior to the transfer to INC Biostatistics. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied).

Laboratory values will be graded following the NCI CTCAE grades version 4.03 where applicable. If no grading exists, values will be classified as 'low'/'normal'/'high' based on laboratory normal ranges, where normal ranges exist. Shift tables for CTCAE grades and normal ranges will be presented.

Summary statistics (mean, median, standard deviation, minimum, maximum and number of observations) will be presented for all continuous assessments. For urinalysis parameters, any quantitative assessments will be summarized for all subjects using the number of subjects with results of negative, trace or positive. In general, any quantitative assessments will be summarized for all subjects using the number and percentage of subjects with the given result. Percentages will be calculated out of the number of subjects with non-missing data.

Shift tables for hematology and clinical chemistry from baseline CTCAE grade to the maximum grade on treatment for each test will be provided. Subjects with both a non-missing baseline and at least one non-missing post-baseline grade will be included. Unscheduled data will be included in "worst post-baseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per subject then the highest grade will be summarized.

For non-CTCAE gradable haematology and biochemistry tests, a shift table will be provided showing shifts relative to the normal ranges. This summary of normal range category changes illustrates the number and percentage of subjects who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the planned time normal range category and the worst-case on-therapy normal range category. Only laboratory tests which cannot be graded per CTCAE v4.03 specified criteria will be included.

Subjects with missing baseline value are to be assumed to have normal baseline value since worst-case can be either 'High' or 'Low'. If a subject has a 'Decrease to Low' and an 'Increase to High' during the same time interval, then the subject is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a subject was 'High' at baseline and decreases to 'Low' during the time interval, the subject is counted in the 'Decrease to Low' category. Likewise, if a subject was 'Low' at baseline and increases to 'High' during the time interval, the subject is counted in the 'Increase to High' category. Subjects are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range 'High' and no normal range 'Low' values during the time interval;
- 'High' at baseline and do not change to 'Low' during the time interval;
- 'Low' at baseline and do not change to 'High' during the time interval.

If any clinically significant findings are identified from the safety lab assessments or thyroid function tests, 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 the start of dosing must be checked against the study inclusion and exclusion (safety lab assessments only) criteria (see Section 3.1 and Section 3.2 of the Protocol).

All laboratory results in original and SI units will be included in data listings. Tests will be listed in alphabetical order. A separate listing for abnormal lab values (Grade 3 and higher and low/high values) will be presented.

Pregnancy test data, including the date/time of collection and the result, will be displayed separately, and listed only.

11.5. VITAL SIGNS

All subjects in the Safety Set will be included in the vital signs analysis.

Vital signs will be captured at each visit and will include measurement of resting heart rate (beats/min), seated systolic and diastolic blood pressure (mmHg), body temperature (°C) and respiratory rate (breaths/minute). On Pembrolizumab dosing days (Cycle 1 Day 1 and Cycles 2-35), vital signs will be taken both pre-dose and at the end of infusion.

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 (see Protocol Section 3.2).

Vital signs data (absolute values and changes from baseline) will be summarized using descriptive statistics by visit and time point for each vital sign parameter.

Baseline for vital signs will be the result prior to the first dose of study treatment. Absolute change from baseline will be calculated for the post dose time points. Absolute change from baseline is calculated as the result at visit minus the baseline result.

All vital signs data will be listed chronologically and summarized by parameter, visit and time point.

11.6. 12-LEAD ELECTROCARDIOGRAM (ECG)

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. All 12-lead ECGs will be obtained after the subject has been resting in the supine position for at least 10 minutes prior to assessment. For each time point triplicate ECG recordings must be taken less than 5 minutes apart.

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 (see Section 3.2 of the Protocol).

If a subject permanently discontinues BGB324 but continues with monotherapy Pembrolizumab), the last ECG assessment will be performed at the next Pembrolizumab administration.

Patients who have a BGB324 interruption of 14 days for toxicity will require an ECG twice weekly for the 2 weeks following recommencement of BGB324 daily dosing to ensure cardiac safety monitoring whilst BGB324 returns to steady state.

ECG data will be listed overall for all patients in the Safety Set, and a separate listing for any clinically significant findings in ECG values will be provided.

The overall evaluation of the ECG data shall be recorded as ‘Normal’, ’Abnormal, not Clinically Significant (NCS)’ or ‘Abnormal, Clinically Significant (CS)’ and will be summarized by visit. Shifts in the overall results of ECG from baseline to worst on-treatment result will be summarized overall. Also a Categorical analysis of QT interval correction will be presented.

11.7. PHYSICAL EXAMINATION

Physical examination includes height (cm) taken at Screening (summarized with subject demographics) and body weight (kg) at Screening and at the start of each cycle. A full physical examination will be performed at Screening and Day 1 at each cycle, as well as at the final study visit.

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

Body systems will be classified as "Normal", "Abnormal Clinically Significant" and "Abnormal Not Clinically Significant", and abnormalities are described.

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.

Physical examination findings will be fully summarized using descriptive statistics for weight, and using the frequency and percentage of subjects under each classification for each body system. Summary tables will be sorted by parameter and visit.

Physical examination data will also be listed for all subjects in the Safety Set.

11.8. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

ECOG performance status will be assessed at Screening, Cycles 2-35 and at the post-treatment visit. Patients must be confirmed as having an ECOG performance status of 0 or 1 at Screening in order to be eligible for study participation.

A summary table will be provided with the number and percentages of patients with each ECOG score (0 to 5) at each study visit.

All ECOG data shall also be listed for all patients in the Safety Set.

11.9. ECHOCARDIOGRAPHY (OR MUGA)

An echocardiography (or MUGA) assessment will be performed at Screening, and after every 6 months (i.e., every 8 cycles thereafter: Cycle 9, Day 1; Cycle 17, Day 1; Cycle 25, Day 1; Cycle 33, Day 1) whilst a patient receives BGB324.

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

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

The following information shall be collected and listed only for all patients in the Safety Set:

- Date of assessment;
- Assessment method;
- Left ventricular ejection fraction (%);
- Results of assessment;
- Abnormality.

12. INTERIM ANALYSES

12.1. DATA REVIEW COMMITTEE

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 subjects.

A Data Review Committee (DRC), consisting of Principal Investigators, the Sponsors' (BerGenBio and Merck) Medical Monitors, and invited experts as required, will review all subject safety data after 6 subjects have been enrolled and had the potential to be followed for 6 weeks (2 cycles), and then again after a further 6 subjects (total 12 subjects) 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 subjects) the DRC will evaluate the need for dose modification for individual subjects, or BGB324 loading or daily dose modification. A rate of >66% (4 or more) of subjects 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.

12.2. INTERIM ANALYSIS

An interim analysis will be performed after 28 evaluable subjects 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 results will constitute the basis for the decision on the start of stage 2.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

No changes are planned from the analysis described in the protocol.

14. REFERENCE LIST

1. Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials. Controlled Clinical Trial 1989; 10:1-10.

2. Tan and Xiong. A flexible multi-stage design for phase II oncology trials. Pharm Stat, 2011. 10(4):369-73.

15. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 or later (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

15.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs. Or a separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word rtf format.
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 guidance
- Naming conventions:
    - Listings: List_16_x_x_shortname.rtf
    - Tables: Tab_14_x_x_shortname.rtf
    - Figures: Fig_14_x_x_shortname.rtf

15.2. TABLE, LISTING AND FIGURE FORMAT

15.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for all TLFs will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no colour), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display maths symbols (e.g. µ). Certain subscripts and superscripts (e.g. cm2) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output should have the following header at the top left of each page:
  BerGenBio ASA BGBC007
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the corresponding TFL output).
- The program name and date should appear as the last footer on each page.

15.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

15.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified;
- Numbers containing fractional portions are decimal aligned.

15.2.5.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

- Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000).

Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

15.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

16. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010.01 and 03.013.01 provide an overview of the development of such SAS programs.

INC Research SOP 03.009.01 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

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