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Clinical Study Protocol

Study Protocol Number:	E7389-M001-218
Study Title:	ENHANCE 1: An Open-Label, Single-Arm, Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination With Pembrolizumab in Subjects With Metastatic Triple-Negative Breast Cancer (mTNBC)
Sponsor.	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA
Investigational Product Names:	Eribulin mesylate (E7389) and pembrolizumab (MK-3475)
Indication:	Metastatic Triple-Negative Breast Cancer (mTNBC)
Phase:	1b/2
Approval Dates:	27 Apr 2015 (Original Protocol) 03 Aug 2016 (Amendment 01) 26 Sep 2016 (Amendment 02) 11Sep 2017 (Amendment 03) 29 May 2018 (Amendment 04) 26 Jun 2020 (Amendment 05)
IND Number:	113851
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure

of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Protocol Amendment 05

Date: 26 June 2020

Change	Rationale	Affected Protocol Sections
The overall study duration was changed from approximately 48 to 60 months and November 2020 was added as the expected time for completion of study (ie, last subject expected to complete the study).	Revised to provide updated information based on current study milestones.	• Synopsis – Study Period and Phase of Development
The End of Study is clarified to refer to the last subject's last visit/assessment (or the end of the 90-day follow up for serious adverse events [SAEs]/events of clinical interest [ECIs]), after which all subjects will have completed their Off-Treatment visit. It is also clarified that as of this amendment (Protocol Amendment 05), Follow-Up assessments in the Posttreatment Phase will not be performed after the subject completes the Off-Treatment visit assessments.	To revise and clarify the End of Study definition to be the the last subject's last visit/assessment (or the end of the 90-day follow up for SAEs]/ECIs). Also, to clarify that as of this amendment, no posttreatment follow-up assessments will be performed.	• Clinical Protocol Synopsis Study Design • Section 9.1 • Section 9.1.3
The recommended Phase 2 dose (RP2D; eribulin 1.4 mg/m^2 IV on Day 1 and Day 8 with pembrolizumab 200 mg IV on Day 1 of each 21-day cycle) determined during Phase 1b part of the study was added.	To specify that the dose assessed during the Phase 1b part of the study based on Cycle 1 dose-limiting toxicities was the determined RP2D.	• Clinical Protocol Synopsis Study Design • Section 9.1
Added text to clarify that for subjects experiencing prolonged clinical benefit, temporary interruption of study treatment for up to 3 months may be permitted after discussion with the treating physician and sponsor. Also, added that after such interruption, the investigators are strongly encouraged to rescan the subject to rule out interim disease progression.	New information to provide additional treatment and scanning guidance for subjects experiencing prolonged clinical benefit.	• Clinical Protocol Synopsis – Duration of Treatment • Section 9.4.1
Added text to specify that after the last subject enrolled in the study has completed 35 cycles of pembrolizumab treatment, all ongoing subjects will be transitioned off study. Additionally, it was clarified that subjects still receiving eribulin monotherapy at that time may continue to receive eribulin off study through their pharmacy (if commercially available for that individual subject) or through a patient assistance program administered by the sponsor. Further, it was clarified that prior to transitioning ongoing subjects to commercial eribulin or an access program, eribulin investigational product will be provided to the ongoing subjects and they	To allow for all ongoing subjects to be transitioned off study, but provide a mechanism for subjects still receiving eribulin at the end of study to be transferred to commercial eribulin supply outside the study or through an access program. To clarify that all ongoing subjects receiving eribulin will continue to receive eribulin study treatment	• Clinical Protocol Synopsis – Duration of Treatment • Section 9.1.3 • Section 9.4.1 • Section 9.5.5

will continue to be assessed according to the study Schedule of Procedures/Assessments until they have had their Off-Treatment visit.	until their Off-Treatment visit and will continue to be assessed according to the study Schedule of Assessments, prior to their transition to commercial eribulin or an access program.	
The duration of monitoring after the first year of follow-up for subjects who discontinued therapy without disease progression was changed from 'every 12 (±1) weeks' to 'every 9 to 12 (±1) weeks per standard of care' until start of new anticancer treatment, disease progression, death, or end of study.	To revise the follow-up imaging schedule for monitoring disease status for subjects who discontinued therapy without disease progression to follow the local standard of care after the first year of follow-up.	• Clinical Protocol Synopsis – Assessments (Efficacy) • Section 9.3.3 • Section 9.5.1.4.1 • Section 9.5.1.4.2 • Section 9.5.2.1 (Table 8 footnote n) • Section 12 (Appendix 4)
Added note to clarify that as of this amendment (Protocol Amendment 05), tumor assessment scans will no longer be sent to the independent core imaging laboratory for efficacy assessment.	No requirement to send tumor assessment scans to independent imaging laboratory following completion of the final efficacy analysis.	• Clinical Protocol Synopsis – Assessments (Efficacy) • Section 9.5.1.4.1 • Section 9.5.1.4.2 • Section 12 (Appendix 4)
Added text to clarify that as of this amendment (Protocol Amendment 05), thyroid function assessment will be done at the discretion of the investigator.	To allow for thyroid function assessment to be done at the investigator's discretion.	• Section 9.5.1.6.3 (Table 7 footnote a) • Section 9.5.2.1 (Table 8 footnote i)
Revised text in statistical and analytical plans section on extent of study treatment exposure analysis in relation to analysis and presentation of extent of exposure data for pembrolizumab.	Updated information to clarify study treatment exposure analysis and data presentation.	• Section 9.7.1.8.1

Revisions to Amendment 04 of the Protocol

Date: 29 May 2018

Change	Rationale	Affected Protocol Section
Enrollment is extended for Stratum 2 to recruit a total of at least 100 evaluable subjects (total of 170 subjects enrolled)	To assess the precision of the ORR point estimate and confidence intervals	• Protocol Synopsis • Section 9.1 • Section 9.3 • Section 9.7.1.6.1 • Section 9.7.2

Change	Rationale	Affected Protocol Section
Updated pembrolizumab background information	The background was updated to reflect the PK/ADA data available	• Section 7.1
Added dose modification guidelines for Myocarditis and redefined All other immune-related AEs	The dose modification information was updated to reflect current data and label information	• Section 9.4.1.2, Table 4
Additional information about study removal of subjects	To clarify the criteria to be considered prior to removing a subject from the study	• Section 9.4.6.3
Updated definition of clinically stable criteria	Administrative change to incorporate pembrolizomab standard language that was not previously listed in the protocol.	• Section 9.5.1.4.2
Clarified discontinuation criteria	Clarification of the criteria for pembrolizumab discontinuation	• Section 9.5.5

Protocol Amendment 3 changes are being made to the Protocol Amendment 1 document. Although Protocol Amendment 2 adding a urothelial cancer cohort was drafted and submitted to the FDA for review it was not issued to the sites or implemented.

Revisions to Amendment 03 of the Protocol

Date: 11 Sep 2017

Change	Rationale	Affected Protocol Section
The overall duration of the study is extended from 24 to 38 months.	To allow time for recruitment of additional subjects in Stratum 2	• Clinical Protocol Synopsis
Enrollment is extended for Stratum 2 to recruit a total of 80 evaluable subjects (total of 150 subjects enrolled)	To provide more consistent and robust clinical data (related with the current promissory results obtained) to justify the possibility to obtained a conditional approval during the next FDA Type B meeting	• Clinical Protocol Synopsis Study Design, sample Size rationale • Section 9.1 • Section 9.3 • Section 9.7.2
The study interval is extended from Dec. 2017 to May 2018.	To allow time for recruitment of additional	• Clinical Protocol Synopsis

Change	Rationale	Affected Protocol Section
	subjects in Stratum 2	
A secondary objective to evaluate efficacy in subjects previously treated with 1 to 2 lines of systemic anticancer therapy in a metastatic setting was added. (Clinical Benefit Rate)	To better estimate efficacy in Stratum 2	• Clinical Protocol Synopsis • Section 8.2
ORR was added as a primary objective in Phase 2 of the study.	To evaluate objective response rate in subjects with metastatic triple-negative breast cancer previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting.	• Clinical protocol Synopsis • Section 8.1
The primary objectives for the 2 phases of the study were updated to include subjects with mTNBC previously treated with 0 Stratum 1 or 1 to 2 (Stratum 2) lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab.		• Clinical protocol Synopsis • Section 8.1
ORR was to be evaluated per RECIST 1.1 by IIR in Stratum 2 subjects in Phase 2 of the study and compared with the historical response rate of pembrolizumab monotherapy of 10%.	Updated due to clinical interest in ORR in Stratum 2 subjects in comparison with historical pembrolizumab monotherapy response rate	• Clinical protocol Synopsis • Section 8.1
Exclusion criterion #14 was modified to include severe hypersensitivity (≥ Grade 3) to pembrolizumab or its excipients.	To clarify the exclusion criteria based on new safety language provided by Merck	• Clinical protocol Synopsis • Section 9.3.2
Exclusion Criterion #16 was modified to exclude subjects with a diagnosis of immunodeficiency or who is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.	To clarify the exclusion criteria based on new safety language provided by Merck	• Clinical Protocol Synopsis • Section 9.3.2
Duration of treatment was clarified to note subjects can receive up to 35 treatments (~2 years) with pembrolizumab until discontinued due to confirmed CR treatment for at least 8 cycles with pembrolizumab and have had at least 2 treatments with pembrolizumab beyond date initial CR was declared	To better define the duration and discontinuation of pembrolizumab treatment	• Clinical Protocol Synopsis • Section 9.5.5
Exploratory endpoint of time to response (TTR)	This endpoint is considered	• Clinical Protocol

Change	Rationale	Affected Protocol Section
was added.	of clinical interest.	Synopsis • Section 8.3 • Section 9.7.1.1.3
The Full Analysis Set (FAS) noted to be used for analysis of PFS and OS.	PFS was added to get a more conservative estimation	• Clinical Protocol Synopsis • Section 9.7.1.2
Bayesian PP no longer used for continuous monitoring of efficacy and futility.	Study will not be stopped for either	• Clinical Protocol Synopsis • Section 9.7.1.6.1
Exploratory efficacy outcomes were further evaluated in the PD-L1 positive set after a cutoff point was determined using external data.	This language was moved to the next section for clarity.	• Clinical Protocol Synopsis • Section 9.7.1.6.3
Clinical Experience with Pembrolizumab was updated.	Section updated per latest language provided by Merck	• Section 7.1.3.2
Procedure for dose modification and management of toxicities (infusion reactions) of pembrolizumab during treatment was updated.	Section updated per latest language provided by Merck	• Section 9.4.1.2 • Section 9.4.6.1 • Table 5
IRRECIST was used after the initial radiologic progression and the use of RECIST 1.1 was adapted to account for the unique tumor response seen with immunotherapeutic drugs.	Updated per current irRECIST guidelines	• Clinical Protocol Synopsis Efficacy Analysis • Section 9.5.1.4.2 • Table 6
The acceptable liver function tests for ALT and AST were clarified in inclusion criterion #8	Updated to reflect industry standard criteria for subjects with liver metastases	• Clinical Protocol Synopsis • Section 9.3.1
Independent imaging review was used for assessment of ORR (primary objective) and other objectives PFS, DOR, CBR and TTR. ORR, PFS, DOR CBR and TTR, based on investigator/local radiology assessment, could also be secondary endpoints.	Updated per FDA guidance regarding tumor assessment for registrational studies	• Clinical Protocol Synopsis • Section 9.5.1.4 • Section 8
CBR, defined as the proportion of subjects who had BOR of CR, PR, or stable disease of ≥24 weeks, was deleted as an exploratory endpoint and added as a secondary endpoint.	Upgraded CBR to secondary objectives due to clinical interest.	• Clinical Protocol Synopsis • Section 9.7.1.1.2
The indication for pembrolizumab was clarified to include other tumor types, package insert.	Updated per latest pembrolizumab package insert	• Section 7.1

Change	Rationale	Affected Protocol Section
A reference to a Phase 2 study of pembrolizumab as monotherapy for previously treated TNBC was added	Updated per latest pembrolizumab clinical study results	• Section 7.2
Results of pembrolizumab KN086 study were added to Table 1	Updated per latest pembrolizumab clinical study results	• Section 7.2
The duration of monitoring for subjects who discontinued therapy without disease progression was changed from every 12 weeks to every 9 weeks for the first year of follow-up and every 12 weeks until start of new anticancer treatment, disease progression, death, or end of study.	To maintain the imaging schedule that is already in place as part of the protocol, For patients within the 1st year of treatment on study, imaging will be performed every 9 weeks +/- 1 week, and for subjects beyond the 1st year of treatment, imaging will be performed every 12 weeks +/- 1 week	• Clinical Protocol Synopsis • Section 9.5.1.4.1 • Table 6 • Section 9.5.2.1, Table 8, Footnote 'n'
A 2-sided Clopper-Pearson test was added to assess CBR, a secondary efficacy analysis.	Updated due to CBR being changed to a secondary objective.	• Section 9.7.1.6.2
Moved Phase 1b safety run-in cohort used for assessing subjects for dose-limiting toxicity (DLT) in the first cycle and to study safety of the 2-drug combination from Primary Efficacy Analysis to Safety Analyses.	This analysis is more appropriate in the safety analyses section rather than the primary efficacy	• Clinical Protocol Synopsis • Section 9.7.1.8
Updated sub-section headings to Primary Efficacy Endpoints, Secondary Efficacy Endpoints and Exploratory Efficacy Endpoints	Updated sub-section headings for clarity	• Clinical Protocol Synopsis • Section 9.7.1.1

Protocol Amendment 2 adding a urothelial cancer cohort was drafted and submitted to the FDA for review. However, Amendment 02 was not issued to the sites or implemented.

Revisions to Amendment 02 of the Protocol

Date: 26 Sep 2016

Change	Rationale	Affected Protocol Section
The strata include first-line subjects who are cisplatin ineligible based on renal impairment (creatinine clearance calculated by Cockcroft-Gault method <60ml/min), grade 2 hearing loss (stratum 1) and subjects who have progressed within 12 months of treatment with a platinum containing regimen [cisplatin or carboplatin or novel platinum] in either the		• Synopsis, Study Design • Section 9.1 • Section 9.4.3

Change	Rationale	Affected Protocol Section
metastatic or perioperative setting (stratum 2). Approximately 40% and 60% of subjects will be enrolled from strata 1 and 2, respectively.		
mUC cohort: up to 50 evaluable mUC subjects will be enrolled in the study. ORR in the historical control is assumed to be 30%. The ORR in this study is estimated as 50%, which is deemed a clinical meaningful improvement. The null and alternative hypotheses are set as follows:		• Synopsis, Primary Efficacy Parameter • Section 9.7.1.6.1
The strata include subjects first-line subjects who are cisplatin ineligible based on renal impairment (creatinine clearance calculated by Cockcroft-Gault method <60ml/min), grade 2 hearing loss (stratum 1) and subjects who have progressed within 12 months of treatment with a platinum containing regimen [cisplatin or carboplatin or novel platinum] in either in the metastatic or perioperative setting (stratum 2). The 2 strata will have approximately 40% (stratum 1) and 60% (stratum 2) of the total subjects.		• Synopsis, Sample Size Rationale • Section 9.7.2
Number of study sites increased from 25 to 30	Will help to ensure that protocol-specified sample size is achieved within study timelines	• Clinical Protocol synopsis • Section 6 • Section 9.3
Revised the study sample size (including evaluable number of subjects) and strata allocation.	There is clinical interest to have a more precise estimation of the response	• Clinical Protocol Synopsis • Section 9.1 • Section 9.3 • Section 9.4.3 • Section 9.7.1.6.1 • Section 9.7.2
Inclusion Criteria #2 Added text	Provides additional clarification for sites with respect to:	• Clinical Protocol synopsis • Section 9.3.1
Text revised that describes reasons for discontinuation from the study.	The eCRF does not collect “primary” and “secondary” reasons for discontinuation. Unnecessary to name eCRF form being used to collect study disposition, so such text is deleted.	• Section 9.3.3 • Section 9.5.5 • Section 9.6.2
Included new text for supportive care guidelines with respect to the use of corticosteroids and revised specific text regarding rescue medications	Updated to remain consistent with the latest pembrolizumab protocol	• Section 9.4.6.1

Change	Rationale	Affected Protocol Section
for treatment of pembrolizumab-related toxicities.	template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016	
Added text "Treatment with bisphosphonates and/or denosumab will be allowed for subjects with bone metastases."	Text added to provide guidance to sites regarding allowed concomitant medications for subjects with bone metastases	• Section 9.4.6
Prohibited Concomitant Therapies and Drugs: Changed to "Systemic glucocorticosteroids for any purpose other than to modulate symptoms of suspected immunologic etiology" Changed to "For subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor."	Text revised to provide clarification for use of corticosteroids in any instance of suspected immunologic etiology. Text revised to provide more specific guidance with regard to continuation of study medication under circumstances that require use of prohibited concomitant medications.	• Section 9.4.6.3
Text revised and/or added regarding the return of or destruction of unused study medication	Original text was not consistent with the Eisai protocol template language and is now revised.	• Section 9.4.8
Revised text for serum and urine pregnancy testing (protocol version 1.0, Table 8 changed to protocol version 2.0, Table 7).	Clarification that pregnancy testing is allowed using either serum or urine β-hCG.	• Section 9.5.1.2 • Table 7 • Schedule of Procedures/ Assessments
Added new text "SAEs and ECIs will be collected for 90 days after the last dose or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. An AE will not be reported on the Adverse Event CRF if other anticancer treatment is started. All SAEs will be reported on the Adverse Event CRF."	Updated to clarify collection timeframe for SAEs and ECIs (see revised ECI definition Section 9.5.4.3.2)	• Section 9.5.1.6.1 • Section 9.5.4.1
Deleted text regarding definition of Events of Clinical Interest; Deleted the protocol version 1.0, Table 7 (and renumber subsequent remaining tables); Deleted protocol version 1.0, Appendix 8 ("Pembrolizumab Events of Clinical Interest Guidance")	Merck notified Eisai that the ECI guidance document has been retired.	• Section 9.5.1.6.2
Laboratory Measurements: Text added to better define sample collection windows for all visits	Clarification of blood draw (hematology, chemistries) and urinalysis windows for C1D1 and all subsequent visits	• Section 9.5.1.6.3 • Schedule of Procedures/ Assessments • Table 7

Change	Rationale	Affected Protocol Section
Various text additions and revisions to Schedule of Procedures/Assessments (added ECG assessments at C1D1 and C1D8; revised footnote 'd'; revised footnote 'f')	Revisions made to keep consistency with text changes in protocol body. Footnote 'd' revised to clarify that subjects may need repeat pregnancy test at Baseline (to be consistent with Exclusion Criteria #11	• Schedule of Procedures/ Assessments (Footnotes 'd' and 'f")
Changed text to "Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported."	Clarification of reporting timeframes for pregnancy to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.2
Revised text for section describing reporting of AEs associated with study drug overdose, misuse, abuse, or medication error.	Eisai protocol template standard language included to emphasize that overdose will not be captured as an AE. Instead, AEs associated with drug overdose, misuse, abuse, and medication error will be captured as an AE and also reported using SAE reporting procedures. Also, the definition of pembrolizumab overdose was updated in latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.3.1
Text revised to indicate that certain liver function test values (ALT, AST, total bilirubin, and alkaline phosphatase) will remain as the only Events of Clinical Interest for the trial.	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.3.2
Text deleted that describes the Data Management Plan.	This text considered to be unnecessary for the protocol and is deleted.	• Section 9.6.2
Updated table for Bayesian Stopping Boundaries	In association with increased sample size, the table in this Appendix is	• Appendix 1

Change	Rationale	Affected Protocol Section
	expanded to include Bayesian stopping boundaries for up to 100 evaluable subjects.	
Deleted text "20 mm by chest x ray"	Although this is standard RECIST per the paper it is not acceptable to follow chest lesions by x-ray alone and any chest imaging must be computed tomography. The only acceptable use of x-ray is for the detection of a new lesion. Therefore, text was removed.	• Appendix 3
Changed to "For this study, similar to that allowed for RECIST 1.1, irRECIST allows the site to select up to 5 target lesions at baseline, 2 per organ …" Changed to "Identify up to 5 lesions, not more than 2 from 1 organ system…"	To clarify that RECIST 1.1 criteria for allowed number of target lesions will be followed throughout the study.	• Appendix 4
Title and contents of protocol version 1.0, Appendix 8 ("Pembrolizumab Events of Clinical Interest Guidance") changed to "Breast Cancer TNM Staging System"	Disease stage is being collected (Demographics and Other Baseline Characteristics) during this study, therefore Screening Assessments is revised to reflect this requirement and new Appendix 8 (Breast Cancer TNM Staging System) is provided in the protocol for reference.	• Appendix 8 • Section 9.5.1.2 • Schedule of Procedures/ Assessments • Section 9.7.1.4

Revisions to Amendment 01 of the Protocol

Date: 03 Aug 2016

Change	Rationale	Affected Protocol Section
Number of study sites increased from 10 to 25.	Will help to ensure that protocol-specified sample size is achieved within study timelines	• Clinical Protocol synopsis • Section 6 • Section 9.3
Revised the term "chemotherapy" to "systemic anticancer therapy" in several sections and defined further in Study Design and Inclusion Criteria #2.	To provide principle investigators clarity for determining eligibility based on the number of lines of therapy used by the subject prior to Screening.	• Clinical Protocol Synopsis • Section 7.1 • Section 8.1 • Section 9.1 • Section 9.3

Change	Rationale	Affected Protocol Section
		• Section 9.3.1 • Section 9.4.3
Revised the study sample size (including evaluable number of subjects) and strata allocation.	There is clinical interest to have a more precise estimation of the response rate for Stratum 2. Therefore, the sample size was increased, allowing for additional Stratum 2 enrollment, and thus increase the statistical power for this cohort of subjects. Other numbers related to change of sample size (eg, number of evaluable subjects) are also updated.	• Clinical Protocol Synopsis • Section 9.1 • Section 9.3 • Section 9.4.3 • Section 9.7.1.6.1 • Section 9.7.2
Inclusion Criteria #2 Changed to: "Metastatic triple-negative breast cancer (confirmed from most recent tissue sample) meeting the following criteria: a. Estrogen receptor (ER) and progesterone receptor (a tumor is ER and/or progesterone receptor positive if at least 1% of the cells examined have estrogen and/or progesterone receptors) and human epidermal growth factor receptor 2 (HER2)-negative (defined as immunohistochemistry [IHC] <2+ or fluorescence in situ hybridization [FISH] negative). b. Previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy."	Provides additional clarification for sites with respect to: a. The cut-off for ER/PR receptor positive. b. Determination of eligibility based on the number of lines and types of therapy used by subject prior to Screening.	• Clinical Protocol synopsis • Section 9.3.1
Exclusion Criteria #2 Changed to "Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment."	Revised to remain consistent with the latest pembrolizumab template provided by Merck ("Pembrolizumab Text for") Eisai PN150 06-Jun-2016	• Clinical Protocol synopsis • Section 9.3.2
Exclusion Criteria #4 Changed to "Current enrollment in another interventional clinical study…"	Clarification that the intention is to exclude those on interventional	• Clinical Protocol synopsis • Section 9.3.2

Change	Rationale	Affected Protocol Section
	studies (not observational, long term follow-up studies).	
Exclusion Criteria #15 Changed to "Scheduled for major surgery during the study."	Updated to simplify and clarify.	• Clinical Protocol synopsis • Section 9.3.2
Exclusion Criteria #17 Changed to "Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis."	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016	• Clinical Protocol synopsis • Section 9.3.2
Exclusion Criteria #20 Changed to "Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted."	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016	• Clinical Protocol synopsis • Section 9.3.2
Added text that tumor assessments are to be performed every 9 weeks ±1 week after the start of study treatment (or sooner if there is evidence of progressive disease).	Clarification of text describing timing of tumor assessments if there is evidence of progressive disease.	• Clinical Protocol synopsis • Section 9.5.1.4.1 • Schedule of Procedures/ Assessments
ECG assessments (both before and after eribulin infusion) at Baseline/C1D1 and C1D8 have been included in the safety assessments.	One Screen Visit determination for ECG may be insufficient in order to confirm the safety profile or detect any safety alert (eg, QTc prolongation) of the eribulin plus pembrolizumab combination.	• Clinical Protocol synopsis • Section 9.5.1.6.6 • Schedule of Procedures/ Assessments
Revised definition for the Evaluable Analysis Set	Using the modified evaluable analysis set will more accurately estimate the primary efficacy endpoint (ORR).	• Clinical Protocol synopsis • Section 9.7.1.2
Updated description of clinical experience with Pembrolizumab	Revised to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for" Eisai PN150 06-	• Section 7.1.3.2

Change	Rationale	Affected Protocol Section
	Jun-2016).	
Text revised that describes reasons for discontinuation from the study.	The eCRF does not collect "primary" and "secondary" reasons for discontinuation. Unnecessary to name eCRF form being used to collect study disposition, so such text is deleted.	• Section 9.3.3 • Section 9.5.5
Added text to clarify exactly when study drugs should be initially administered, and added text to provide guidance for correction of hypokalemia and/or hypomagnesemia prior to first dose of eribulin.	To provide clarification for when to administer first dose of study drugs; To provide guidance that is consistent with the eribulin mesylate Package Insert regarding correction of hypokalemia and hypomagnesemia prior to initiation of eribulin.	• Section 9.4.1
Added text "Note: If institutional guidelines require BSA recalculation starting at 5% or more weight change, this will be acceptable."	Text added to allow sites more flexibility and consistency with their institutional guidelines.	• Section 9.4.1
Changed text associated with guidance for study drug administration (eg, timing and treatment windows clarified)	Clarification provided to ensure that study drug treatment guidelines are strictly followed.	• Section 9.4.1 • Section 9.4.5 • Schedule of Procedures/ Assessments
Text and table amended for eribulin dose delays and modifications.	Eribulin dose delays and modifications revised to be more consistent with Package Insert guidance.	• Section 9.4.1.1 • Table 3
Updated Dose Modification Guideline for Pembrolizumab-Related Adverse Events	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016	• Section 9.4.1.2 • Table 4
Included new text for supportive care guidelines with respect to the use of corticosteroids and revised specific text regarding rescue medications for treatment of pembrolizumab-related toxicities.	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016	• Section 9.4.6.1

Change	Rationale	Affected Protocol Section
Added text "Treatment with bisphosphonates and/or denosumab will be allowed for subjects with bone metastases."	Text added to provide guidance to sites regarding allowed concomitant medications for subjects with bone metastases	• Section 9.4.6
Prohibited Concomitant Therapies and Drugs: Changed to "Systemic glucocorticosteroids for any purpose other than to modulate symptoms of suspected immunologic etiology" Changed to "For subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor."	Text revised to provide clarification for use of corticosteroids in any instance of suspected immunologic etiology. Text revised to provide more specific guidance with regard to continuation of study medication under circumstances that require use of prohibited concomitant medications.	• Section 9.4.6.3
Text revised and/or added regarding the return of or destruction of unused study medication	Original text was not consistent with the Eisai protocol template language and is now revised.	• Section 9.4.8
Revised text for serum and urine pregnancy testing (protocol version 1.0, Table 8 changed to protocol version 2.0, Table 7)	Clarification that pregnancy testing is allowed using either serum or urine β-hCG.	• Section 9.5.1.2 • Table 7 • Schedule of Procedures/ Assessments
Added new text "SAEs and ECIs will be collected for 90 days after the last dose or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. An AE will not be reported on the Adverse Event CRF if other anticancer treatment is started. All SAEs will be reported on the Adverse Event CRF."	Updated to clarify collection timeframe for SAEs and ECIs (see revised ECI definition Section 9.5.4.3.2)	• Section 9.5.1.6.1 • Section 9.5.4.1
Deleted text regarding definition of Events of Clinical Interest; Deleted the protocol version 1.0, Table 7 (and renumber subsequent remaining tables); Deleted protocol version 1.0, Appendix 8 ("Pembrolizumab Events of Clinical Interest Guidance")	Merck notified Eisai that the ECI guidance document has been retired.	• Section 9.5.1.6.2
Laboratory Measurements: Text added to better define sample collection windows for all visits.	Clarification of blood draw (hematology, chemistries) and urinalysis windows for C1D1 and all subsequent visits	• Section 9.5.1.6.3 • Schedule of Procedures/ Assessments • Table 7
Various text additions and revisions to Schedule of	Revisions made to keep	• Schedule of

Change	Rationale	Affected Protocol Section
Procedures/Assessments (added ECG assessments at C1D1 and C1D8; revised footnote 'd'; revised footnote 'f')	consistency with text changes in protocol body. Footnote 'd' revised to clarify that subjects may need repeat pregnancy test at Baseline (to be consistent with Exclusion Criteria #11	Procedures/ Assessments (Footnotes 'd' and 'f')
Changed text to "Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported."	Clarification of reporting timeframes for pregnancy to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.2
Revised text for section describing reporting of AEs associated with study drug overdose, misuse, abuse, or medication error.	Eisai protocol template standard language included to emphasize that overdose will not be captured as an AE. Instead, AEs associated with drug overdose, misuse, abuse, and medication error will be captured as an AE and also reported using SAE reporting procedures. Also, the definition of pembrolizumab overdose was updated in latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.3.1
Text revised to indicate that certain liver function test values (ALT, AST, total bilirubin, and alkaline phosphatase) will remain as the only Events of Clinical Interest for the trial.	Updated to remain consistent with the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN150 06-Jun-2016").	• Section 9.5.4.3.2
Text deleted that describes the Data Management Plan.	This text considered to be unnecessary for the protocol and is deleted.	• Section 9.6.2

Change	Rationale	Affected Protocol Section
Updated table for Bayesian Stopping Boundaries	In association with increased sample size, the table in this Appendix is expanded to include Bayesian stopping boundaries for up to 100 evaluable subjects.	• Appendix 1
Changed confirmatory scans for SD to occur at least 8 weeks after initial response.	The confirmation of response for stable disease was required at a minimum of 5 weeks after initial response incorrectly. This minimum time period was corrected to be 8 weeks and is now consistent throughout the protocol.	• Appendix 3
Deleted text "20 mm by chest x ray"	Although this is standard RECIST per the paper it is not acceptable to follow chest lesions by x-ray alone and any chest imaging must be computed tomography. The only acceptable use of x-ray is for the detection of a new lesion. Therefore, text was removed.	• Appendix 3
Changed to "For this study, similar to that allowed for RECIST 1.1, irRECIST allows the site to select up to 5 target lesions at baseline, 2 per organ …" Changed to "Identify up to 5 lesions, not more than 2 from 1 organ system…"	To clarify that RECIST 1.1 criteria for allowed number of target lesions will be followed throughout the study.	• Appendix 4
Title and contents of protocol version 1.0, Appendix 8 ("Pembrolizumab Events of Clinical Interest Guidance") changed to "Breast Cancer TNM Staging System"	Disease stage is being collected (Demographics and Other Baseline Characteristics) during this study, therefore Screening Assessments is revised to reflect this requirement and new Appendix 8 (Breast Cancer TNM Staging System) is provided in the protocol for reference.	• Appendix 8 • Section 9.5.1.2 • Schedule of Procedures/ Assessments • Section 9.7.1.4

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7389, MK-3475

Name of Active Ingredients: Eribulin mesylate and pembrolizumab

Study Protocol Title

ENHANCE 1: An Open-Label, Single-Arm, Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination With Pembrolizumab in Subjects With Metastatic Triple-Negative Breast Cancer (mTNBC)

Investigators

To be determined

Sites

Approximately 25 study sites in the United States (US)

Study Period and Phase of Development

Phase: Phase 1b/2

Duration Overall: Approximately 60 months

Duration by Subject: Estimated median treatment duration is 6 months, although subjects may remain on study treatment as long as the subject demonstrates clinical benefit.

Study Interval: The original study enrollment was estimated to begin in August 2015 and end in or before February 2017. The study enrollment is being extended with Protocol Amendment 4 to recruit a total of at least 100 evaluable subjects in Stratum 2 (approximately 170 total subjects) by October 2018. Based on the current status of subjects ongoing on study as of Protocol Amendment 05, the last subject is expected to complete the study by November 2020.

Objectives

Primary Objectives

In subjects with metastatic triple-negative breast cancer (mTNBC) previously treated with 0 (Stratum1) or 1 to 2 (Stratum 2) lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab:

- For the Phase 1b part – to determine safety and tolerability of eribulin mesylate in combination with pembrolizumab in all subjects (ie, Stratum 1 and 2).
- For the Phase 2 part – to evaluate objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by independent imaging review (IIR) in all subjects.
- For the Phase 2 part – to evaluate ORR per RECIST 1.1 by IIR in Stratum 2 subjects and compare with the historical response rate of pembrolizumab monotherapy of 10%.

Secondary Objectives

- For the Phase 2 part, in all subjects and separately in Stratum 2 subjects, to evaluate progression-free survival (PFS) per RECIST 1.1 by IIR.
- To evaluate overall survival (OS).
- To evaluate duration of response (DOR) per RECIST 1.1 by IIR.
- To evaluate clinical benefit rate (CBR) per RECIST 1.1 by IIR.

- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by investigator review.
- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by IIR and OS outcome by PD-L1 (programmed death receptor-ligand 1) expression.
- To evaluate the safety and tolerability of the combination.

Exploratory Objectives

- To evaluate time to response (TTR) per RECIST 1.1 by IIR in all subjects and separately in Stratum 2 subjects.
- To evaluate exposure-response relationship in all subjects.
- To explore potential effects of pembrolizumab co-administration on the pharmacokinetics (PK) of eribulin mesylate in all subjects.
- To explore efficacy outcomes (ORR, PFS, DOR, and CBR) per immune-related RECIST 1.1 (irRECIST) by IIR and investigator review for all subjects and separately in Stratum 2 subjects.

Study Design

This is an open-label, single-arm, multicenter, Phase 1b/2 study of eribulin mesylate in combination with pembrolizumab in subjects with metastatic triple-negative breast cancer previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Subjects may have received prior neo/adjuvant chemotherapy.

The Phase 1b part includes 1 initial safety run-in cohort in which at least 6 subjects will receive eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (Dose Level 1). Dose-limiting toxicity (DLT) will be assessed in the first cycle. Dose level 1 can be selected as the recommended Phase 2 dose (RP2D) if no more than 1 subject has a DLT. Otherwise, eribulin mesylate dose will be lowered from 1.4 mg/m^2 to 1.1 mg/m^2 on Days 1 and 8 of a 21-day cycle (Dose Level 0). If no more than 1 out of 6 subjects at Dose Level 0 has a DLT, the Phase 2 part will proceed with Dose Level 0. Approximately 12 subjects may be enrolled in the Phase 1b part of the study.

As of Protocol Amendment 05, the RP2D was determined to be eribulin 1.4 mg/m^2 IV administered on Day 1 and Day 8 of each 21-day cycle with pembrolizumab 200 mg IV administered on Day 1 of each 21-day cycle.

Under Protocol Amendment 1, 107 subjects (including subjects in Phase 1b who are on RP2D level) were enrolled in 2 strata and received the same combination treatment at the RP2D level. The strata include no prior systemic anticancer therapy in the metastatic setting (Stratum 1) and previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting (Stratum 2). Bayesian predictive probability (PP) of response rate was used to monitor the response rate after postbaseline tumor assessments for at least 38 subjects were available. The study could be stopped early for efficacy or futility if PP crosses the prespecified boundary. Hence, efficacy conclusion of the primary efficacy endpoint of ORR could be made on the basis of the predictive probability prior to the full enrollment of 100 evaluable subjects in the study (see Statistical Methods for details).

There is clinical interest to have a more precise estimation of the efficacy data for Stratum 2. Therefore, per Protocol Amendment 3, additional subjects will be added to Stratum 2 in order to include a total of 80 evaluable subjects in Stratum 2 for final analysis. As a result, approximately 150 subjects in total (145 evaluable with 80 in Stratum 2) will be enrolled. Per Protocol Amendment 4, 20 additional subjects will be added to Stratum 2 in order to include a total of at

least 100 evaluable subjects in Stratum 2 for final analysis.

Pharmacokinetic (PK) assessments of eribulin mesylate will be performed in all subjects in the Phase 1b part of the study. Subjects in the Phase 2 part will undergo sparse PK sampling for population pharmacokinetic/pharmacodynamic (PK/PD) analysis where feasible.

The last subject last assessment is the **End of Study**, which will be the date of the End-of-Treatment visit (or the end of the 90-day follow up for serious adverse events [SAEs]/events of clinical interest [ECIs]) for the last subject. As of Protocol Amendment 05, the Follow-Up asessments in the Posttreatment Phase will no longer need to be performed.

Number of Subjects

A total of approximately 170 adult female or male subjects previously treated with 0 to 2 lines of systemic anticancer therapy in the metastatic setting will be enrolled (including at least 6 subjects from the Phase 1b part). It is estimated that 165 of the 170 subjects will be evaluable for the primary analysis.

Inclusion Criteria

1. Females or males, aged ≥18 years at the time of signing the informed consent form (ICF)
2. Metastatic triple-negative breast cancer (confirmed from most recent tissue sample) meeting the following criteria:
    a. Estrogen receptor (ER) and progesterone receptor negative (a tumor is ER and/or progesterone receptor positive if at least 1% of the cells examined have estrogen and/or progesterone receptors) and human epidermal growth factor receptor 2 (HER2) -negative (defined as immunohistochemistry [IHC] <2+ or fluorescence in situ hybridization [FISH] negative).
    b. Previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy.
3. Presence of measureable disease meeting the following criteria:
    a. At least 1 lesion of ≥10 mm in long axis diameter for nonlymph nodes or ≥15 mm in short axis diameter for lymph nodes that is serially measurable according to RECIST 1.1 using computerized tomography or magnetic resonance imaging or panoramic and close-up color photography.
    b. Lesions that have had radiotherapy must show subsequent radiographic evidence of increased size to be deemed a target lesion.
4. Life expectancy of ≥3 months
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
6. Adequate renal function as evidenced by serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥50 mL/minute according to the Cockcroft and Gault formula
7. Adequate bone marrow function, defined as:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Hemoglobin (Hb) ≥10.0 g/dL (can be corrected by growth factor or transfusion)
    c. Platelet count $\geq 100 \times 10^9$/L
8. Adequate liver function, defined as:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN)
    b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN unless there are bone metastases, in which case liver specific alkaline phosphatase must be separated from the total and used to

assess the liver function instead of the total alkaline phosphatase. ALT and AST ≤ 5 × ULN if subject has liver metastases

9. Resolution of all chemotherapy-related or radiation-related toxicities to Grade 1 severity or lower, except for stable sensory neuropathy (≤ Grade 2) and alopecia
10. Archived tissue sample or new biopsy sample
11. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
12. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).
13. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, a combination oral contraceptive (estrogen/progesterone), or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 120 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 120 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 120 days after study drug discontinuation.
14. Males who have had a successful vasectomy (confirmed azoospermia) or they and their female partners meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 120 days after study drug discontinuation). No sperm donation is allowed during the study period or for 120 days after study drug discontinuation.
15. Willing and able to comply with all aspects of the treatment protocol
16. Provide written informed consent.

Exclusion Criteria

1. Previous treatment with eribulin mesylate or any anti-PD-1, PD-L1, or PD-L2 agent
2. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.
3. Less than 6 months since prior adjuvant chemotherapy
4. Current enrollment in another interventional clinical study or used any investigational drug or device within the past 28 days preceding informed consent
5. Treatment with chemotherapy or biological therapy within the previous 3 weeks, radiation or small molecule targeted therapy within the previous 2 weeks
6. Known central nervous system (CNS) disease, except for those subjects with treated brain

metastasis who are stable for at least 1 month, having no evidence of progression or hemorrhage after treatment and no ongoing requirement for corticosteroids, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period.

7. Known history of human immunodeficiency virus (HIV) positive
8. Known active hepatitis B (eg, HBsAg reactive) or hepatitis C (eg, HCV RNA detected).
9. Existing anticancer treatment-related toxicities of Grades ≥2 (except for alopecia and Grade 2 sensory neuropathy) according to Common Terminology Criteria for Adverse Events (CTCAE v4.03)
10. Any other malignancy that required treatment or has shown evidence of recurrence (except for nonmelanoma skin cancer, or histologically confirmed complete excision of carcinoma in situ) during the 5 years prior to enrollment in this study
11. History of significant cardiovascular disease, defined as:
    a. congestive heart failure greater than New York Heart Association (NYHA) Class II according to the NYHA Functional Classification
    b. unstable angina or myocardial infarction within 6 months of enrollment
    c. serious cardiac arrhythmia
12. Clinically significant electrocardiogram (ECG) abnormality, including a marked Baseline prolonged QT/QTc ([QT interval/corrected QT interval], eg, a repeated demonstration of a QTc interval >500 ms)
13. History of concomitant medical conditions or infectious diseases that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study
14. Hypersensitivity to the active substance or any other excipients of the eribulin mesylate drug product, or severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients
15. Scheduled for major surgery during the study
16. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
17. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
18. Has a history of interstitial lung disease
19. Has an active infection requiring systemic therapy
20. Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.
21. The investigator's belief that the subject is medically unfit to receive eribulin mesylate and pembrolizumab or unsuitable for any other reason

Study Treatments

Investigational drugs: Combination doses will be investigated in 1 cohort. Eribulin mesylate 1.4 mg/m^2 via IV injection over 2 to 5 minutes administered on Day 1 and Day 8 and pembrolizumab 200 mg via IV infusion over 30 minutes administered on Day 1 (21-day cycle). Alternative doses may be explored to identify the RP2D prior to the start of the Phase 2 part if necessary. The eribulin mesylate dose may be reduced/ delayed; the pembrolizumab dose may be

delayed per protocol in the event of toxicity**.**

Comparator Drug: Not applicable.

Dose Delays and Modifications: Dose delays and modifications for toxicities associated with eribulin mesylate and pembrolizumab are described in detail in Section 9.4.1.1 and Section 9.4.1.2, respectively.

Duration of Treatment

Subjects will be treated with eribulin mesylate and pembrolizumab and can remain on one or both study drugs in the presence of clinical benefit until intercurrent illness, unacceptable toxicity, or disease progression occurs, or until the subject withdraws consent.

For subjects experiencing prolonged clinical benefit, temporary interruption (up to 3 months) of study treatment may be permitted after discussion with the treating physician and the sponsor. After such interruption, investigators are strongly encouraged to rescan the subject to rule out interim progression of disease.

Subjects can receive up to 35 treatments (approximately 2 years) with pembrolizumab. During that time, subjects may continue until disease progression, unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy for the subject, or sponsor's decision to terminate the study.

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 8 cycles (24 weeks) with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

After the last subject has completed 35 cycles of pembrolizumab or has discontinued pembrolizumab for other reasons, all ongoing subjects will be transitioned off study. Subjects still receiving eribulin monotherapy at this time may continue to receive eribulin treatment off study through their pharmacy (if commercially available for that individual subject) or through a patient assistance program administered by the sponsor. Subjects will continue to receive eribulin investigational product and will continue to be assessed according to the Schedule of Procedures/Assessments until they complete the End-of-Treatment visit, prior to their transition to commercial eribulin or an access program.

Concomitant Drug/Therapy

Permitted therapy: includes but is not limited to granulocyte colony-stimulating factor (G-CSF).

Excluded therapy: includes other investigational drugs/devices.

Rescue Medications for pembrolizumab and management of infusion reactions associated with the use of pembrolizumab are described in detail in Section 9.4.6 (Prior and Concomitant Therapy).

Assessments

Definition of Dose-Limiting Toxicity:

A DLT is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to either of the study drugs.

Hematologic Toxicities:

- Any Grade 4 thrombocytopenia or neutropenia lasting >7 days

Nonhematologic Toxicities:

- Episcleritis, uveitis, or iritis of Grade 2 or higher
- Any Grade 4 toxicity
- Any Grade 3 toxicity EXCLUDING:

- Nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours
- Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
- Transient Grade 3 AST or ALT elevation, defined as no more than 3 days with or without steroid use

- Discontinuation or delay of more than 2 weeks of either study drug due to treatment-related AE will be considered as a DLT

All subjects enrolled in Phase 1b will be assessed for DLTs during a DLT assessment window of the first cycle of 21 days. Subjects who discontinue study treatment prior to completing the DLT assessment window for any reason other than a DLT will be replaced.

Efficacy

Tumor assessment will be performed by the investigator based on both RECIST 1.1 and irRECIST. Copies of all tumor assessment scans will be sent to an imaging core laboratory designated by the sponsor for independent review of efficacy assessment. Note: As of Protocol Amendment 05, tumor assessment scans will no longer be sent to an independent imaging core laboratory. Detailed methodology for assessment by independent review will be provided in an Independent Imaging Review Charter. Tumor assessments are to be performed every 9 weeks ± 1 week after the start of study treatment (or sooner if there is evidence of progressive disease) using consistent imaging methodology (ie, computed tomography [CT] scan/magnetic resonance imaging [MRI] or bone scan and consistent use or nonuse of contrast media). In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks ± 1 week during Year 1, and every 9 to 12 weeks ± 1 week thereafter according to standard of care, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first. In addition, overall survival (OS) status (disposition) will be assessed throughout the study.

Treatment After Initial Radiologic Progression

Pembrolizumab, like other immunotherapeutic agents, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of image responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

For any subject who showed first radiologic evidence of progressive disease (PD) and is deemed clinically stable, it is at the discretion of the investigator to continue treating the subject until progression is confirmed at least 4 weeks from the date of the first radiologic evidence of PD. If progression is confirmed, the subject will be discontinued from study treatment. Otherwise, the subject will continue treatment and radiographic scans. Any subject who had initial radiologic progression and is deemed clinically unstable should be discontinued from both study drugs and no subsequent scan for confirmation is required.

Safety:

Safety and tolerability will be evaluated by the following assessments:

- Adverse events (AEs), serious adverse events (SAEs), drug-related AEs, AEs leading to discontinuation, drug-related AEs leading to discontinuation reported by the investigator (coded according to the current version of the Medical Dictionary for Regulatory Activities [MedDRA], graded according to the National Cancer Institute [NCI] CTCAE Grades 0 to 5), and collected throughout the study. All AEs must be followed for 30 days after the

subject's last dose, or until resolution, or the start of new anticancer therapy, whichever comes first. SAEs and must be followed for 90 days and events of clinical interest (ECIs) must be followed for 30 days (see Section 9.5.1.6.2) after the subject's last dose of study drug or, if the subject initiates new anticancer therapy, for 30 days following the last dose, whichever is earlier. All SAEs and ECIs should be followed to resolution or, if resolution is unlikely, to stabilization.

- Laboratory safety tests, which should be reviewed prior to pembrolizumab and eribulin mesylate administration. Hematology will be assessed on Days 1 and 8 of every cycle, serum chemistry will be assessed on Day 1 of every cycle, and urinalysis will be assessed on Day 1 at Cycles 2 and 4.
- An electrocardiogram (ECG) performed at screening, and on Day 1 and Day 8 of Cycle 1.
- Physical examinations (symptom-directed) performed throughout study.
- Vital signs performed throughout study.
- ECOG PS (assessed every cycle)

The schedule of efficacy and safety assessments performed in the study is presented in Table 8, Schedule of Procedures/Assessments.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Bioanalytical Methods

Plasma concentrations of eribulin mesylate will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Statistical Methods

RECIST 1.1 criteria will be used in the evaluation of tumor status for the primary, secondary and exploratory endpoints, irRECIST criteria will be used in the evaluation of tumor status for the exploratory endpoints. Tumor response data obtained per RECIST 1.1 by IIR will be utilized in the main analysis of ORR, PFS and DOR. In addition, tumor assessment data assessed per RECIST1.1 by investigator review and per irRECIST by IIR and investigator review will be considered as secondary or exploratory.

Study Endpoints

Primary Efficacy Endpoint

- Objective Response Rate (ORR) – defined as the proportion of subjects who had BOR of CR or partial response (PR).

Secondary Efficacy Endpoints

- Progression-Free Survival (PFS) – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first
- Overall Survival (OS) – defined as the time from the date of first dose of study drug until date of death from any cause
- Duration of Response (DOR) – defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR.
- Clinical Benefit Rate (CBR)– defined as the proportion of subjects who had BOR of CR, PR, or durable stable disease (SD) (≥24 weeks)
- Estimates of ORR, PFS, OS, DOR and CBR in the PD-L1 Positive Set.

Exploratory Efficacy Endpoints

- Time to response (TTR) - defined as the time from the date of first dose of study drug to

the first documented CR or PR for those subjects with a confirmed PR or CR.

- ORR, PFS, DOR, and CBR using irRECIST

All above endpoints based on tumor measurement will be assessed according to RECIST 1.1, unless otherwise specified.

Analysis Sets

- The DLT Evaluable Set includes subjects who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate with no more than 1 dose reduction and at least 1 dose of pembrolizumab) and have sufficient safety evaluation. Subjects who had a DLT event will be considered evaluable for the dose-limiting toxicity as well. It is the analysis set for DLT evaluation in the Phase 1b part of the study.
- The Full Analysis Set (Safety Analysis Set) includes all subjects who received any amount of either study drug. This is the analysis set for safety analyses and analysis of PFS and OS.
- The Evaluable Analysis Set (subset of Full Analysis Set) includes all subjects who have both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early or death. It is the analysis set for efficacy analyses.
- The PD-L1 Positive Set (subset of Evaluable Analysis Set) includes evaluable subjects whose PD-L1 expression level is above the threshold that is to be specified prior to the final analysis. Key primary and secondary efficacy endpoints (ie, ORR, PFS, OS, DOR and CBR) will be summarized in this analysis set.

Efficacy Analyses

Primary Efficacy

Approximately 165 evaluable subjects on RP2D will be enrolled in the study, including phase 1b and 2.

Bayesian Predictive Probability (PP) design was used in original study design. Under original design, in the combined Stratum 1 and 2 subjects, the ORR value per RECIST 1.1 by IIR was assumed to be 0.20 for the historical control based on the recent studies (Table 1). The ORR in this study is estimated to be 0.35. Under protocol amendment 1, approximately 100 evaluable subjects were expected to be enrolled, Bayesian PP was used to monitor the response rate after postbaseline tumor assessments of at least 38 subjects were available. Tumor response data per RECIST 1.1 by investigator review were used for continuous monitoring. The calculation of PP is based on the goal of claiming superiority of the combination at the end of the study if

$$P(p>0.2|data)\geq 0.95 \quad (1)$$

where p was the response rate of the combination, 0.2 was the response rate of historical control, based on single-agent pembrolizumab and eribulin mesylate in recent studies; 0.95 was the prespecified target probability (θ_T) and P(p>0.2|data) was the posterior probability. On the basis of the accumulated data thus far in the study, the probabilities of all possible future outcomes that lead to equation (1) at the end of the study would be added in order to obtain the predictive probability. Therefore, early decision of study termination prior to reaching approximately 100 evaluable subjects was possible for claiming the combination is promising when PP is above a prespecified upper threshold (θ_U) or for claiming futility when PP is below a prespecified lower threshold (θ_L). The upper and lower cutoff probabilities for decision making, θ_U and θ_L, were set as 0.99 and 0.025. Under the predictive monitoring, the study proceeded as follows:

If PP> θ_U(=0.99), stop the study and claim the combination promising

If PP< θ_L(=0.025), stop the study and claim the combination not promising

Otherwise, continue the study until the number of evaluable subjects reaches to 100

See Section 9.7.1.6.1 for more details of the Bayesian stopping boundaries. After completion of enrollment under protocol amendment 1, Bayesian PP is no longer used for continuous monitoring of efficacy and futility as the study will not be stopped early for either efficacy or futility.

Under protocol amendment 3, in Stratum 2 subjects, the hypotheses for ORR per RECIST by IIR are updated to be H_0: ORR=0.10 vs. Ha: ORR=0.25, based on the most recent pembrolizumab monotherapy KN086 study (Table 1). Therefore, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2 to provide >90% power for the comparison of H_0: ORR=0.10 vs. Ha: ORR=0.25 at 1-sided alpha value of 0.025 using a binomial exact test. Under protocol amendment 4, additional subjects will be enrolled to ensure at least 100 evaluable subjects are enrolled in Stratum 2 to obtain a more precise estimate of ORR.

Final Analysis

In all evaluable subjects (i.e., Stratum 1 and 2), Bayesian Posterior probability in equation (1) will be evaluated to determine the efficacy after the tumor response status has been collected from the last evaluable subjects. That is, to claim efficacy if P ($p>0.2|data$) ≥ 0.95. A 2-sided 95% credible interval of objective response rate in the evaluable subjects will be constructed to aid the interpretation of the results Details of predictive and posterior probabilities calculation will be provided in the Statistical Analysis Plan (SAP).

In the evaluable Stratum 2 subjects, a binomial exact test will be used to test the estimated ORR versus a historical response rate of 10% at 1-sided alpha value of 0.025.

Subjects in the Phase 1b part who were treated at the RP2D and were deemed evaluable will be combined with Phase 2 subjects in the efficacy analysis.

Secondary Efficacy

PFS, OS, and DOR

Progression-free survival (PFS), OS, and DOR will be analyzed using Kaplan-Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS, OS, and DOR at 6 and 12 months will be presented with 2-sided 95% confidence intervals (CIs) if estimable. Censoring rules for PFS and DOR will be provided in the SAP.

The cumulative PFS, OS, and DOR will be plotted over time. The median and first and third quartiles from Kaplan–Meier estimation for PFS, OS, and DOR will be provided with 95% CIs if estimable.

Clinical Benefit Rate

A 2-sided Clopper–Pearson 95% CI will be constructed for calculating exact binomial intervals.

Exploratory Efficacy

In addition to RECIST1.1, tumor assessment data (ie, ORR, PFS, DOR, and CBR) will be assessed using irRECIST in the sensitivity analysis.

The analysis of time to response (TTR) will follow the analysis of PFS. The analysis will be performed in the subjects with confirmed PR/CR per RECIST1.1 by IIR.

All efficacy analyses will be performed in all subjects and separately for each stratum.

Efficacy outcomes will be further evaluated in the PD-L1 Positive Set after a cutoff point is determined with external data. The clinical utility of PD-L1 as a predictive marker in mTNBC subjects who receive eribulin mesylate and pembrolizumab combination treatment will be assessed.
In addition to RECIST1.1, tumor assessment data (ie, ORR, PFS, DOR, and CBR) will be assessed

using irRECIST in the sensitivity analysis.

Safety Analyses

RP2D and DLT

The Phase 1b study will include at least 1 safety run-in cohort in which 6 metastatic triple-negative breast cancer (mTNBC) subjects who receive eribulin mesylate 1.4 mg/m^2 on Days 1 and 8 and pembrolizumab 200 mg on Day 1 of a 21-day cycle (Dose Level 1). Subjects will be observed for dose-limiting toxicity (DLT) in the first cycle. The purpose of the safety run-in cohort(s) is to study safety of the 2-drug combination. The Phase 2 part will proceed with Dose Level 1 when no more than 1 subject has a DLT. Otherwise, a lower eribulin mesylate dose of 1.1 mg/m^2 and pembrolizumab 200 mg will be evaluated in another cohort of 6 subjects. If no more than 1 subject has a DLT in the first cycle, the Phase 2 part will proceed with Dose Level 0 as the RP2D. Otherwise, alternative doses (eribulin mesylate 0.7 mg/m^2) will be explored prior to the start of the Phase 2 part.

The DLT rate will be summarized descriptively at each combination dose level. Subsequent DLTs will be reported and summarized as well.

Adverse Events

The incidence of treatment-emergent adverse events throughout the study (graded according to NCI CTCAE 4.03) will be coded according to MedDRA and descriptively summarized overall, by grade, seriousness, action taken on study drug (including discontinuation and dose modification), and outcome for the Full Analysis Set (Safety Analysis Set).

General Safety

- Hematology, serum chemistry and qualitative urinalysis laboratory analyses will be summarized descriptively for observed values, by grade, and by change from Baseline by cycle.
- Vital sign variables (body temperature, heart rate, blood pressure, and body weight) will be summarized descriptively for observed values, by grade, and change from Baseline.
- Physical examination results determined by the investigator to be clinically significant will be reported as an adverse event
- ECOG performance status will be summarized descriptively for observed values, by grade, and by change from Baseline.

Interim Analyses

Under Protocol Amendment 1, interim decisions could be made based on the expected response rate at the end of the study, which compromises the current information with the future sample size via predictive probability approach. The Bayesian design can continuously update the predictive probability of the study outcome, such that early termination of a study was possible for either superiority or futility. One interim analysis was performed after the first 39 enrolled subjects completed at least 2 post-baseline tumor assessments or discontinued due to PD or death.

Under Protocol Amendment 3, Bayesian PP continuous monitoring will not be applied.

Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetics

Plasma concentrations of eribulin mesylate will be analyzed to determine PK parameters including maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), clearance (CL), area under the concentration-time curve (AUC), and terminal elimination phase half-life ($t_{½}$). These PK parameters will be calculated at a minimum and additional parameters will be calculated

if the data allow.

Pharmacokinetic–Pharmacodynamic: Eribulin mesylate PK/PD analysis will be conducted to evaluate the relationship between exposure and efficacy and exposure and safety when eribulin mesylate is coadministered with pembrolizumab. Exploratory graphical analysis will be conducted for PK/PD evaluations and may be followed by model-based analysis. Further details will be provided in a separate document.

Sample Size Rationale

A total of approximately 170 subjects (at least 165 evaluable with 100 in Stratum 2) will be enrolled.

Under Protocol Amendment 1, 107 subjects including at least 6 from the Phase 1b part were enrolled in the study. Enrollment was split into 2 strata, which include first-line (Stratum 1) versus second- and third-line (Stratum 2) subjects. Bayesian predictive probability was used to monitor the study after response data from the first 38 subjects were available. Sample size calculation was carried out assuming the historical response rate of 0.2. Using simulation, the model parameters (θ_L=0.025, θ_U =0.99, and θ_T=0.95) were calibrated such that the frequentist 1-sided Type I error was 0.0326 when the tumor response rate in the combination regimen was 0.2 (under frequentist's null hypothesis H_0), and the power was 0.9278 when the response rate was 0.35 (under frequentist's alternative hypothesis H_a). The expected numbers of subjects needed to reach the decisions were 56 and 61 when p=0.2 (under H_0) and 0.35 (under H_a), respectively. A vague beta prior distribution for response rate, p, was specified in PP calculation; that is, p~beta (0.2, 0.8). PP was updated for every 3 new subjects in the simulations, which mimics the group sequential decision-making in a real study setting. Without Bayesian interim monitoring, the Type I error was estimated as 0.0358, and power was estimated as 0.9418 in demonstrating posterior probability P(p>0.2|data) ≥0.95. Five thousand simulations were run to estimate these design characteristics.

Per Amendment 3, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2. Using binomial exact test, the power is 0.92 with 80 evaluable subjects to demonstrate statistical significance at 1-sided alpha of 0.025 for the assumptions of H_0: ORR=0.10 vs. Ha: ORR=0.25. With 80 subjects, the 95% confidence interval for ORR from binomial distribution will be 0.160-0.359 if the observed ORR is 0.25. Per Amendment 4, additional subjects will be enrolled to ensure 100 evaluable subjects in Stratum 2. With 100 subjects, power will be increased to 98% and the 95% confidence interval for ORR from binomial distribution will be 0.169-0.347 if the observed ORR is 0.25.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
ß -hCG	beta-human chorionic gonadotropin
BOR	best overall response
BSA	body surface area
CA	Competent Authority
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CL	Clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP	cytochrome-P450
DCR	disease control rate
DDI	drug-drug interaction
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity

Abbreviation	Term
DOR	duration of response
ECG	Electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EMT	epithelial mesenchymal transition
ER	estrogen receptor
FDA	US food and drug administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Hb	Hemoglobin
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
G-CSF	granulocyte colony-stimulating factor
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
irAE	immune-related adverse events
irCR	immune-related complete response
irPD	immune-related progressive disease
IIR	independent imaging review
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	Intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLT	Lower level term
mAb	monoclonal antibody

Abbreviation	Term
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTNBC	metastatic triple-negative breast cancer
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death receptor-ligand 1
PET-CT	positron emission tomography-CT
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PFS	progression-free survival
PP	predictive probability
PR	partial response
PS	performance status
PT	preferred term
Q3W	every 3 weeks
QT/QTc	QT interval/corrected QT interval
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors (version 1.1)
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
T4	Thyroxine
$t_{½}$	terminal elimination phase half-life

Abbreviation	Term
TEAE	treatment-emergent adverse event
T1DM	Type 1 diabetes mellitus
t_{max}	time to maximum plasma concentration
TNBC	triple negative breast cancer
TNM	Tumor-Node-Metastases
TPC	Treatment of Physician's Choice
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WHO	World Health Organization

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and Federal Regulations, Title 21 Code of Federal Regulations (CFR) Part 56. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or the sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the data cutoff for the final statistical analysis. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he or she may withdraw from the study at any time, and that withdrawal of consent will not affect his or her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his or her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, Federal Regulations, Title 21 CFR Part 50, and any applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site. Subjects will be asked to sign either a separate ICF for pharmacokinetic (PK) assessments or provide consent for PK assessments within the main ICF. Subjects may also be asked to sign either a separate ICF or provide consent within the main ICF to allow the sponsor to request scans of their tumor assessments for central review.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 25 investigational sites in the United States (US).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

This is an open-label, single-arm multicenter Phase 1b/2 study to evaluate the efficacy and safety of eribulin mesylate in combination with pembrolizumab in subjects with metastatic triple-negative breast cancer (mTNBC) previously treated with 0 to 2 lines of systemic anticancer therapy in the metastatic setting.

Eribulin mesylate (HALAVEN®) is a microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting (HALAVEN package insert).

Pembrolizumab (KEYTRUDA®) is a potent, humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

Pembrolizumab is also being investigated for treatment of mTNBC. Results of "A Phase 1b Study of Pembrolizumab in Patients with Advanced Triple-Negative Breast Cancer" indicated that it is effective and safe in this population (Nanda, et al., 2014).

This study will evaluate whether this combination results in better efficacy than eribulin mesylate or pembrolizumab monotherapy and provides an acceptable safety profile in treating the mTNBC patient population.

7.1.1 Current Therapeutic Options

Triple negative breast cancer (TNBC) is a challenging disease with the poorest prognosis of all breast cancer subtypes. Importantly, there are currently no known molecular targets for this subgroup. Cytotoxic chemotherapy is the only systemic treatment option for patients with mTNBC. To identify a targeted anticancer agent effective against mTNBC in combination with chemotherapy is a major unmet need in breast cancer treatment.

7.1.2 Eribulin Mesylate

7.1.2.1 Mechanism of Action of Eribulin Mesylate

Direct Cytotoxicity

Halichondrin B is a large polyether macrolide isolated from the rare marine sponge *Halichondrin okadai*. It exhibits potent anticancer effects both in vitro and in vivo (Lin, et al., 2000; Wang, et al., 1999; Chang, et al., 1999) with a tubulin-based mechanism that appears to be distinct from all other antitubulin agents (Lin, et al., 2000; Morse, et al., 2005; Rein, et al., 2000). Eribulin mesylate (E7389) is a structurally simplified, synthetic analog of this marine natural product that exhibits similar anticancer properties in preclinical models (Roninson, et al., 2001) through a tubulin-based antimitotic mechanism similar to that of halichondrin B. It is a nontaxane microtubule dynamics inhibitor that suppresses microtubule growth and sequesters tubulin into nonfunctional aggregates, preventing mitotic spindle formation with subsequent G2-M arrest and apoptosis. It exhibited potent anticancer effects in preclinical models of various malignancies, including breast cancer (Lin, et al., 2000; Morse, et al., 2005; Roninson, et al., 2001; Ellis, et al., 1997; Stearns, et al., 2003; Arends, et al., 1990). This mechanism of action is distinct from that of other antitubulins, such that it may be effective in patients with disease that is resistant to these agents. In fact, eribulin mesylate demonstrated antitumor activity in preclinical studies with cell lines that are paclitaxel resistant as a result of beta tubulin mutations (Gauthier, et al., 1996). The in vivo animal model data also predicted that this agent would achieve greater efficacy than the taxanes and with fewer adverse effects.

Effects on Tumor Vascular Remodeling and reversal of EMT in Pre-Clinical Models

It has been reported that the abnormal vasculature present in tumors impairs blood perfusion and oxygenation, leading to hypoxic conditions, which promotes invasion, metastasis, and overall aggressiveness of tumor cells through epithelial mesenchymal transition (EMT)-related processes. Normalization of vascular perfusion is therefore gaining interest as a therapeutic approach to inhibit motility, invasiveness, and aggressiveness of tumor cells. Preclinical data suggest that eribulin mesylate improves tumor blood perfusion through vascular remodeling, which may indirectly contribute to reduced metastasis, invasion, and reversal of EMT in the tumor microenvironment, leading to a normoxic tumor microenvironment (Yoshida, et al., 2014; Funahashi, et al., 2014).

7.1.2.2 Clinical Experience with Eribulin Mesylate

Eribulin mesylate was first approved on 15 Nov 2010 in the US for the treatment of patients with metastatic breast cancer (MBC) who have previously received at least

2 chemotherapeutic regimens for the treatment of metastatic disease. Approval has been obtained in 54 countries.

Overall, approximately 5457 subjects have been enrolled in clinical studies since the Development International Birth Date; approximately 3984 subjects have received eribulin mesylate up to the data lock point of 14 May 2014 (HALAVEN® Investigator Brochure).

Of the total of 1349 serious adverse events (SAEs) reported in subjects who received eribulin mesylate, 510 were assessed by the investigator as related to eribulin mesylate and 839 were reported as unrelated to eribulin mesylate. The most frequent treatment-related SAEs were febrile neutropenia, neutropenia and pyrexia (HALAVEN® Investigator's Brochure).

In summary, eribulin mesylate provides clinical benefit for the treatment of patients with locally recurring breast cancer and MBC previously treated with chemotherapeutic regimens. Eribulin mesylate has an acceptable safety profile. The risk of toxicity with eribulin mesylate is comparable or less than that for other agents currently used in this population. Proposed precautions and dose adjustments will allow the toxicity of eribulin mesylate to be managed appropriately. Eribulin mesylate is provided as a ready-to-use formulation that is easily administered without the need for premedications to prevent hypersensitivity. It is therefore concluded that the benefit-risk ratio of eribulin mesylate continues to be favorable.

7.1.3 Pembrolizumab

7.1.3.1 Mechanism of Action of Pembrolizumab

Immune Restoration

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (Pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (IB).

Refer to the Investigator's Brochure/approved labeling for detailed background information on MK-3475.

7.1.3.2 Clinical Experience with Pembrolizumab

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy studies in subjects with non-small cell lung cancer, head and neck squamous cell carcinoma, urothelial cancer, gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical studies are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure.

The most frequent potential immune-mediated adverse reactions reported in patients treated with pembrolizumab were hypo/hyperthyroidism, pneumonitis, colitis, hepatitis, nephritis, and hypophysitis (KEYTRUDA® Package Insert, Pembrolizumab Investigator's Brochure).

7.2 Study Rationale

There are currently no known molecular targets for mTNBC and cytotoxic chemotherapy is the only systemic treatment option for these patients.

Recent advances in genomics and gene expression profiling have shed new light on the significant heterogeneity within TNBC. In particular, the Cancer Genome Atlas RNA sequencing data was used (Mittendorf, et al., 2014) to show significantly greater expression of the T-cell inhibitory molecule programmed cell death receptor-1 (PD-1) ligand 1 (PD-L1) gene in TNBC (n = 120) compared with non-TNBC (n = 716; P <0.001). Breast tumor tissue microarrays were also evaluated for PD-L1 expression, which was present in 19% (20 of 105) of TNBC specimens.

Pembrolizumab, an anti-PD-1 monoclonal antibody that releases antitumor immune response blocked by the PD-L1 pathway, is being investigated for mTNBC and a preliminary study indicated that it is safe and effective in this population (Nanda, et al., 2014). Preliminary result of a Phase 2 study of pembrolizumab monotherapy for previously treated mTNBC also showed potential efficacy (Adams, et al., 2017).

Eisai clinical studies (Study 305 and Study 301) showed that eribulin mesylate has better efficacy than the Treatment of Physician's Choice (TPC) and capecitabine, respectively, in mTNBC.

Efficacies of Study 305 and Study 301 in mTNBC, as well as a pembrolizumab studies in patients with advanced TNBC, are listed in Table 1.

Table 1 Efficacies of Eisai Study 305 and Study 301 in mTNBC and Pembrolizumab Studies in Advanced TNBC

	Eisai Study 305		Eisai Study 301		Pembrolizumab Study[a]	Pembrolizumab KN086 Study[b]
Patient Population	mTNBC with 2-5 lines of prior chemotherapy		mTNBC with 0-2 lines of prior chemotherapy		Advanced TNBC with ≥0 line of prior chemotherapy	mTNBC with ≥1 line of prior chemotherapy Cohort A
Treatment	Eribulin	TPC	Eribulin	Capecitabine	Pembrolizumab	Pembrolizumab
No. of Patients	84	40	150	134	27	170
Median OS (days)	288	193	439	285	NA	8.9 months
Median PFS (days)	67	57	87	71	57 (1.9 months)	2.0 months
Complete Response	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (3.7%)	0.6%
Partial Response	3 (3.6%)	2 (5.0%)	14 (9.3%)	8 (6.0%)	4 (14.8%)	4%
Stable Disease	32 (38.1%)	12 (30.0%)	76 (50.7%)	61 (45.5%)	7 (25.9%)	21%
Progressive Disease	44 (52.4%)	26 (65.0%)	40 (23.7%)	51 (38.1%)	12 (44.4%)	63%
Not Evaluable/ Unknown	5 (6.0%)	0 (0%)	19 (12.6%)	14 (10.4%)	3 (11.1%)	

mTNBC = metastatic triple-negative breast cancer, OS = overall survival, PFS = progression free survival, TNBC = triple negative breast cancer, TPC = Treatment of Physician's Choice.

a: Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, et al. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. Presented at 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract S1-09.

b: Adams S., et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer mTNBC): KEYNOTE-086 cohort A. (Abstract 1008). Presented at 2017 ASCO Annual Meeting. June 2-6, 2017. Chicago, Illinois.

Eribulin mesylate and pembrolizumab each have a unique mechanism of action (direct cytotoxicity and immune restoration, respectively) and a different safety profile, hence combination therapy with these 2 agents may provide better antitumor outcomes over that seen with either agent alone (Table 1).

In addition to its direct cytotoxicity actions, preclinical data suggest that eribulin mesylate has significant beneficial effects on tumor vascular remodeling that could potentially result in improved tumor blood perfusion. Therefore, eribulin mesylate may lead to increased

pembrolizumab concentrations in tumor tissue and thus indirectly enhance permbrolizumab's antitumor activity in the clinical setting when the 2 drugs are administered simultaneously.

From a safety perspective, the most frequent SAEs associated with eribulin mesylate (eg, neutropenia) and most frequent adverse reactions associated with pembrolizumab (eg, immune-mediated adverse reactions) are not overlapping. Thus, it is not expected that these individual toxicities will be exacerbated with combined use of the 2 drugs.

Therefore, this study combining eribulin mesylate and pembrolizumab may provide a new systematic treatment option for mTNBC.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives for the 2 phases of the study are as follows:

In subjects with metastatic triple-negative breast cancer (mTNBC) previously treated with 0 (Stratum 1) or 1 to 2 (Stratum 2) lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab:

- For the Phase 1b part – to determine the safety and tolerability of eribulin mesylate in combination with pembrolizumab in all subjects (ie, Stratum 1 and 2).
- For the Phase 2 part – to evaluate the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by independent imaging review (IIR) in all subjects.
- For the Phase 2 part – to evaluate ORR per RECIST 1.1 by IIR in Stratum 2 subjects and compare with the historical response rate of pembrolizumab monotherapy of 10%.

8.2 Secondary Objectives

The secondary objectives for the study are as follows:

- For the Phase 2 part, in all subjects and separately in Stratum 2 subjects, to evaluate Progression-Free Survival (PFS) per RECIST 1.1 by IIR
- To evaluate overall survival (OS)
- To evaluate duration of response (DOR) per RECIST 1.1 by IIR
- To evaluate clinical benefit rate (CBR) per RECIST 1.1 by IIR
- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by investigator review
- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by IIR and OS outcome by PD-L1 expression.
- To evaluate the safety and tolerability of the combination

8.3 Exploratory Objectives

The exploratory objectives for the study are as follows:

- To evaluate time to response (TTR) per RECIST 1.1 by IIR in all subjects and separately in Stratum 2 subjects
- To evaluate exposure-response relationship in all subjects
- To explore potential effects of pembrolizumab co-administration on the pharmacokinetics (PK) of eribulin mesylate in all subjects
- To explore efficacy outcomes (ORR, PFS, DOR, and CBR) per immune-related RECIST 1.1 (irRECIST) by IIR and investigator review for all subjects and separately in Stratum 2 subjects

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, single-arm, multicenter, Phase 1b/2 study of eribulin mesylate in combination with pembrolizumab in subjects with metastatic triple-negative breast cancer previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Subjects may have received prior neo/adjuvant chemotherapy.

The Phase 1b part includes 1 initial safety run-in cohort in which at least 6 subjects (up to a maximum of 12) will receive eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (Dose Level 1). Dose-limiting toxicity (DLT) will be assessed in the first cycle. Dose Level 1 can be selected as the recommended Phase 2 dose (RP2D) if no more than 1 subject has a DLT. Otherwise, the eribulin mesylate dose will be lowered from 1.4 mg/ m^2 to 1.1 mg/m^2 on Days 1 and 8 of a 21-day cycle (Dose Level 0). If no more than 1 out of 6 subjects at Dose Level 0 has a DLT, the Phase 2 part will proceed with Dose Level 0. Approximately 12 subjects may be enrolled in the Phase 1b part of the study.

As of Protocol Amendment 05, the RP2D was determined to be eribulin 1.4 mg/m^2 IV administered on Day 1 and Day 8 of each 21-day cycle with pembrolizumab 200 mg IV administered on Day 1 of each 21-day cycle.

Approximately 170 subjects in total (including subjects in Phase 1b who are on RP2D level) will be enrolled in 2 strata and receive the same combination treatment at the RP2D level. The strata include no prior systemic anticancer therapy in the metastatic setting (Stratum 1) and previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting (Stratum 2).

Under Protocol Amendment 1, for the first 100 evaluable subjects enrolled, Bayesian predictive probability (PP) of response rate will be used to monitor the response rate after

postbaseline tumor assessments for at least 38 subjects are available. The study could be stopped early for efficacy or futility if PP crosses the prespecified boundary. Hence, efficacy conclusion of the primary endpoint ORR could be made on the basis of the predictive probability prior to the full enrollment of 100 evaluable subjects in the study (see the Statistical Methods Section 9.7 for details).

Per Protocol Amendment 3, additional subjects will be added to Stratum 2 in order to include a total of 80 evaluable subjects in Stratum 2 for final analysis. Therefore, a total of approximately 150 subjects (145 evaluable with 80 in Stratum 2) will be enrolled.

Per Protocol Amendment 4, 20 additional subjects will be added to Stratum 2 in order to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis. Therefore, a total of approximately 170 subjects (at least 165 evaluable with 100 in Stratum 2) will be enrolled.

Pharmacokinetic assessments of eribulin mesylate will be performed in all subjects in the Phase 1b part of the study. Subjects in the Phase 2 part will undergo sparse PK sampling for population PK/pharmacodynamic (PK/PD) analysis where feasible.

The last subject last assessment is the **End of Study**, which will be the date of the End-of-Treatment visit (or the end of the 90-day follow up for serious adverse events [SAEs]/events of clinical interest [ECIs]) for the last subject. As of Protocol Amendment 05, Follow-Up asessments in the Posttreatment Phase will no longer need to be performed.

9.1.1 Pretreatment Phase

The Pretreatment Phase consists of the Screening Period, which will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

9.1.2 Treatment Phase

The Treatment Phase of the study will begin with the first dose of study drug administration in Cycle 1 and continue in 21-day cycles until completion of the End of Treatment assessments (within 30 days after the last study drug administration) or subject discontinuation, whichever occurs first. In the presence of clinical benefit, subjects will remain on study treatment until intercurrent illness, unacceptable toxicity or disease progression occurs or the subject withdraws consent.

9.1.3 Posttreatment Phase

The Posttreatment Phase consists of the End of Treatment Period and the Follow-Up Period. The End of Treatment Period will occur within 30 days of the final treatment and consists of end of treatment assessments (see Schedule of Procedures/Assessments, Table 8). Subjects

with SAEs and/or ECIs at the time of End of Treatment will be followed for 90 days after the last dose of study drug or, if the subject initiates new anticancer therapy, for 30 days following the last dose of study drug, whichever is earlier.

The Follow-Up Period will begin immediately after the End of Treatment assessments have been completed and will continue as long as the study subject is alive or the study subject withdraws consent. Subjects who discontinue study treatment before disease progression will continue to undergo disease assessment every 12 weeks ±1 week until documentation of disease progression or start of another anticancer therapy. Subjects who are being followed for survival at the time of data cutoff for the primary analysis (ie, at the end of the Treatment Phase) will continue to be followed for survival during the posttreatment Follow-Up Period. Note: As of Protocol Amendment 05, Follow-Up asessments no longer need to be performed.

After the last subject has completed 35 cycles of pembrolizumab, all ongoing subjects will be transitioned off study. Subjects still receiving eribulin monotherapy at this time may continue to receive eribulin treatment off study through their pharmacy (if commercially available for that individual subject) or through a patient assistance program administered by the sponsor. Subjects will continue to receive eribulin investigational product and will be assessed according to the Schedule of Procedures/Assessments (Table 8) until they complete the End-of-Treatment visit, prior to their transition to commercial eribulin or an access program.

The last subject last assessment is the **End of Study**, which will be the date of the End-of-Treatment visit (or the end of the 90-day follow-up for SAEs/ECIs) for the last subject.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is an open-label study in metastatic breast cancer that will evaluate the combination of 2 drugs with proven anticancer activity to determine whether the agents have improved activity with an acceptable toxicity profile. The study design was adapted from previous studies of these agents and may offer a new systematic treatment option for the indication.

The inclusion and exclusion criteria are standard for anticancer studies in the desired population and are designed to enroll subjects who can possibly benefit from treatment and at the same time limit possible harmful effects both to study subjects and to unborn children from unplanned pregnancies.

The key endpoints are standard for cancer studies.

9.3 Selection of Study Population

A total of approximately 170 adult female or male subjects previously treated with 0 to 2 lines of systemic anticancer therapy in the metastatic setting will be enrolled (including at least 6 subjects from the Phase 1b part). It is estimated that 165 (at least 100 in Stratum 2) of the 170 subjects will be evaluable for the primary analysis. Approximately 25 study sites in

the United States will enroll subjects for this study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study.

1. Females or males, aged ≥18 years at the time of signing the informed consent form (ICF)
2. Metastatic triple-negative breast cancer (confirmed from most recent tissue sample) meeting the following criteria:
    a. Estrogen receptor (ER) and progesterone receptor negative (a tumor is ER and/or progesterone receptor positive if at least 1% of the cells examined have estrogen and/or progesterone receptors) and human epidermal growth factor receptor 2 (HER2) -negative (defined as immunohistochemistry (IHC) <2+ or fluorescence in situ hybridization (FISH) negative).

    b. Previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) are not considered forms of systemic anticancer therapy.
3. Presence of measureable disease meeting the following criteria:
    a. At least 1 lesion of ≥10 mm in long axis diameter for nonlymph nodes or ≥15 mm in short axis diameter for lymph nodes that is serially measurable according to RECIST 1.1 using either computerized tomography or magnetic resonance imaging or panoramic and close-up color photography.

    b. Lesions that have had radiotherapy must show subsequent radiographic evidence of increased size to be deemed a target lesion.
4. Life expectancy of ≥3 months
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
6. Adequate renal function as evidenced by serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥50 mL/minute according to the Cockcroft and Gault formula
7. Adequate bone marrow function, defined as:
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Hemoglobin (Hb) ≥10.0 g/dL (can be corrected by growth factor or transfusion)
    c. Platelet count $\geq 100 \times 10^9$/L
8. Adequate liver function, defined as:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN)

b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN unless there are bone metastases, in which case liver specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase. ALT and AST ≤ 5 × ULN if subject has liver metastases

9. Resolution of all chemotherapy- or radiation-related toxicities to Grade 1 severity or lower except for stable sensory neuropathy (≤ Grade 2) and alopecia
10. Archived tissue sample or new biopsy sample
11. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
12. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
13. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, a combination oral contraceptive (estrogen/progesterone), or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 120 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 120 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 120 days after study drug discontinuation.
14. Males who have had a successful vasectomy (confirmed azoospermia) or they and their female partners meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 120 days after study drug discontinuation). No sperm donation is allowed during the study period or for 120 days after study drug discontinuation.
15. Willing and able to comply with all aspects of the treatment protocol
16. Provide written informed consent.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Previous treatment with eribulin mesylate or any anti-PD-1, PD-L1, PD-L2 agent
2. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.
3. Less than 6 months since prior adjuvant chemotherapy
4. Current enrollment in another interventional clinical study or used any investigational drug or device within the past 28 days preceding informed consent
5. Treatment with chemotherapy or biological therapy within the previous 3 weeks, radiation or small molecule targeted therapy within the previous 2 weeks
6. Known central nervous system (CNS) disease, except for those subjects with treated brain metastasis, who are stable for at least 1 month, having no evidence of progression or hemorrhage after treatment and no ongoing requirement for corticosteroids, as ascertained by clinical examination and brain imaging magnetic resonance imaging **[**MRI] or computed tomography [CT]) during the screening period
7. Known history of HIV positive
8. Known active hepatitis B (eg, HBsAg reactive) or hepatitis C (eg, HCV RNA detected)
9. Existing anticancer treatment-related toxicities of Grades ≥2 (except for alopecia and Grade 2 sensory neuropathy) according to Common Terminology Criteria for Adverse Events (CTCAE 4.03)
10. Any other malignancy that required treatment or has shown evidence of recurrence (except for nonmelanoma skin cancer or histologically confirmed complete excision of carcinoma in situ) during the 5 years prior to enrollment in this study.
11. History of significant cardiovascular disease, defined as:
    a. congestive heart failure greater than New York Heart Association (NYHA) Class II according to the NYHA Functional Classification (Appendix 5)
    b. unstable angina or myocardial infarction within 6 months of enrollment
    c. serious cardiac arrhythmia
12. Clinically significant electrocardiogram (ECG) abnormality, including a marked Baseline prolonged QT/QTc interval (eg, a repeated demonstration of a QTc interval >500 ms)
13. History of concomitant medical conditions or infectious disease that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study

14. Hypersensitivity to the active substance or any other excipients of the eribulin mesylate drug product, or severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients
15. Scheduled for major surgery during the study
16. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
17. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
18. Has a history of interstitial lung disease.
19. Has an active infection requiring systemic therapy.
20. Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.
21. The investigator's belief that the subject is medically unfit to receive eribulin mesylate and pembrolizumab or unsuitable for any other reason.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Posttreatment Phase and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Subject Disposition case report form (CRF) page will be completed indicating the reason for discontinuation from treatment. In addition, the date of last dose of study drugs will be recorded on the Study Drug Dosing CRF page.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every every 9 weeks ± 1 week during Year 1, and every 9 to 12 weeks ±1 week thereafter according to standard of care, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

9.4 Treatments

9.4.1 Treatments Administered

Study drugs eribulin mesylate and pembrolizumab will be administered throughout the study as described in Table 2. The study drugs will be administered after all the Inclusion and none of the Exclusion Criteria are met (Section 9.3.1 and Section 9.3.2) and all procedures and assessments have been completed as detailed on the Schedule of Procedures/Assessments (Table 8). Prior to initiating eribulin mesylate on C1D1, correct for hypokalemia and hypomagnesemia and monitor these electrolytes periodically during therapy (Table 7).

Table 2 Treatments Administered

Drug Name	Dose	Dose Form	Infusion Rate	Day/Cycle
Eribulin Mesylate	1.4 mg/m^2	IV infusion	Infused over 2-5 minutes	Day 1 and Day 8 of each 21-day cycle
Pembrolizumab	200 mg	IV infusion	Infused over 30 minutes (-5 min/+10 min range allowed)	Day 1 of each 21-day cycle

IV = intravenous, mg/m^2 = milligram per square meter.

Before dose administration, the amount of eribulin mesylate needed for each subject must be calculated in the following manner:

1. Scheduled dose (mg/m^2) × body surface area (m^2) = Dose (mg)
2. Dose (mg) × 2 = the number of mL of eribulin mesylate to withdraw from vials for administration.

Body surface area (BSA) will be calculated using any method that is accepted and customarily used by the investigational site, such as the Mosteller formula:

$$BSA\ (m^2) = ([Height\ ([cm] \times Weight\ (kg))] / 3600)^{1/2}$$

Height and body weight will be recorded at the screening visit. Thereafter, body weight will be recorded on Day 1 of each treatment cycle to recalculate BSA (in the event that weight has changed by 10% or more*).

*Note: If institutional guidelines require BSA recalculation starting at 5% or more weight change, this will be acceptable.

The amount of eribulin mesylate required (as calculated above) will be withdrawn from the appropriate number of vials into a syringe. This may be administered directly as an intravenous injection over 2 to 5 minutes or diluted in up to 100 mL 0.9% saline for IV

infusion over 2 to 5 minutes. No special tubing is required for IV administration of eribulin mesylate.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

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

Pembrolizumab and eribulin mesylate must be administered on Day 1 of each 21-day cycle; pembrolizumab will be given first and followed immediately by eribulin mesylate.

Eribulin mesylate alone will be administered on Day 8 of each 21-day cycle.

Pembrolizumab and eribulin mesylate may be administered up to 3 days before or after the scheduled Day 1 of each 21-day cycle due to administrative reasons. Correspondingly, eribulin mesylate alone may be administered up to 2 days before or after the scheduled Day 8 of each 21-day cycle due to administrative reasons.

Subjects initially treated with eribulin mesylate and pembrolizumab can remain on 1 or both study drugs in the presence of clinical benefit until intercurrent illness, unacceptable toxicity, or disease progression occurs, or until the subject withdraws consent.

For subjects experiencing prolonged clinical benefit, temporary interruption (up to 3 months) of study treatment may be permitted after discussion with the treating physician and the sponsor. After such interruption, investigators are strongly encouraged to rescan the subject to rule out interim progression of disease. In the event of an AE leading to treatment interruption or delay of either study drug, the subject may continue treatment with the other study drug, as long as there is a clinical benefit.

After the last subject has completed 35 cycles of pembrolizumab, all ongoing subjects will be transitioned off study. Subjects still receiving eribulin monotherapy at this time may continue to receive eribulin treatment off study through their pharmacy (if commercially available for that individual subject) or through a patient assistance program administered by the sponsor. Subjects should continue to receive eribulin investigational product and be assessed according to the Schedule of Procedures/Assessments (Table 8) until they complete the End-of-Treatment visit, prior to their transition to commercial eribulin or an access program.

9.4.1.1 Eribulin Mesylate Dose Modification During Treatment

Eribulin mesylate dose may need to be delayed and reduced during the study. Dose interruption and dose reduction instructions for subjects who experience eribulin mesylate toxicity are presented in Table 3.

Recommended dose delays:

- Do not administer eribulin mesylate on Day 1 or Day 8 for any of the following:

- Absolute neutrophil count (ANC) <1,000/mm^3
- Platelets <75,000/mm^3
- Grade 3 or 4 nonhematological toxicities

- Eribulin mesylate Day 8 dose may be delayed for a maximum of 1 week.
  - If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
  - If toxicities resolve or improve to ≤Grade 2 severity by Day 15, administer eribulin mesylate at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions:

If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin mesylate at a reduced dose as set out in Table 3.

Do not re-escalate the mesylate eribulin dose after it has been reduced.

Table 3 Eribulin Mesylate Dose Adjustments for Toxicity

Adverse Reaction / Toxicity[a]	Eribulin Mesylate Dose Modification
Permanently reduce the 1.4 mg/m^2 eribulin mesylate dose for any of the following: ANC <500/mm^3 for >7 days ANC <1,000/mm^3 with fever or infection Platelets <25,000/mm^3 Platelets <50,000/mm^3 requiring transfusion Non-hematologic Grade 3 or 4 toxicities Omission or delay of Day 8 eribulin mesylate dose in previous cycle for toxicity	1.1 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2 **If unable to administer a scheduled dose of eribulin mesylate for more than 21 days of study, discuss with sponsor prior to continuing treatment**	Discontinue eribulin mesylate

ANC = absolute neutrophil count.

a: Toxicities graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE, v 4.03).

9.4.1.2 Pembrolizumab Dose Modification During Treatment

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 for guidelines regarding dose modification and supportive care.

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

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record

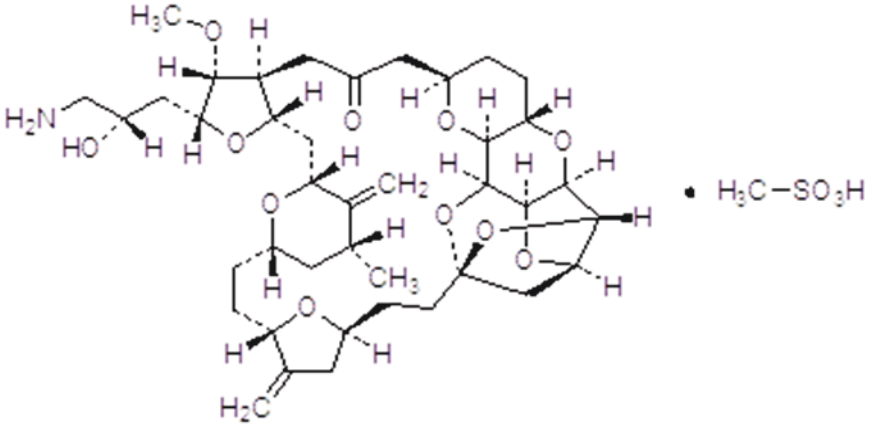
9.4.2 Identity of Investigational Products

The study drugs will be supplied by the sponsor in labeled containers. The final drug will be prepared by the institution's pharmacist. The sponsor will provide the investigational products (eribulin mesylate and pembrolizumab) as open-label supplies. Eribulin mesylate and pembrolizumab will be labeled as investigational product per local regulations and supplied to the clinical site by a third-party vendor. The investigational products will be addressed only to the pharmacist (or designee).

9.4.2.1 Chemical Name, Structural Formula of Eribulin Mesylate

Eribulin mesylate will be supplied to the study sites in glass vials containing 1.0 mg eribulin mesylate in 2.0 mL of clear, colorless, and sterile solution.

- Test drug code: E7389
- Generic name: eribulin mesylate
- Chemical name:
  (2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-2-[(2S)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one methanesulfonate (salt)
- Molecular formula: $C_{40}H_{59}NO_{11}CH_4O_3S$
- Molecular weight: 826.0
- Structural formula:



9.4.2.2 Chemical Name, Structural Formula of Pembrolizumab

Pembrolizumab may be provided as a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial will be reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate-80 (0.4 mg), sucrose (140 mg). The solution may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

- Test drug code: MK-3475
- Generic name: Pembrolizumab
- Chemical name: Humanized X PD-1_mAB (H409A11)IgG4
- Molecular formula: not applicable
- Molecular weight: 149 kDa (approximate)
- Structural formula: not applicable

9.4.2.3 Comparator Drug

Not applicable.

9.4.2.4 Labeling for Study Drugs

Eribulin mesylate and pembrolizumab will be labeled in accordance with text that is in full regulatory compliance with FDA regulations.

The clinical study labels will contain, but are not limited to:

- Name, address, and telephone number of the sponsor
- Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and potency
- Lot number
- Protocol number
- Directions of use (if applicable)
- Storage conditions
- Storage restrictions (if applicable)
- Expiration date (if applicable, and not required for US)
- Caution: New Drug-Limited by Federal (US) Law to Investigational Use

9.4.2.5 Storage Conditions

Study drugs will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drugs are maintained within an established temperature range. The investigator or designee is responsible for

ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all the eligibility requirements (Section 9.3) will be assigned to receive eribulin mesylate in combination with pembrolizumab. There is no randomization in this study. Subjects will be enrolled from 2 strata: no prior systemic anticancer therapy in the metastatic setting and previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting.

9.4.4 Selection of Doses in the Study

The level 1 dose of eribulin mesylate (1.4 mg/m^2 IV on Days 1 and 8 of a 21-day cycle) was selected based on the FDA approved label.

The pembrolizumab dose used in the study of metastatic melanoma was 2 mg/kg every 3 weeks (Q3W) and in advanced TNBC was 10 mg/kg every 2 weeks (Q2W). This study will use a 200 mg Q3W fixed dose. The rationale to use a 200 mg Q3W fixed dose is based on a population PK analysis from 476 subjects with the following findings:

- the relationship between clearance and body weight, with an allometric exponent of 0.59, supports both body weight normalized dosing and a fixed dose across all body weights
- pembrolizumab has a wide therapeutic range (exposure margins of 0.5 – 5.0) based on the melanoma indication
- exposure is similar between melanoma and other solid tumor indications.

Therefore, the 200 mg Q3W fixed dose regimen is likely similar, with regard to efficacy and tolerability, to the 10 mg/kg Q2W dose regimen, and there are no anticipated changes in exposure between different indication settings.

9.4.5 Selection and Timing of Dose for Each Subject

All subjects will receive pembrolizumab first, followed immediately by eribulin mesylate on Day 1 of each cycle. On Day 8 of each cycle, the subjects will receive eribulin mesylate only.

The Phase 1b part includes 1 initial safety run-in cohort in which 6 subjects will receive eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (Dose Level 1). Dose-limiting toxicity will be assessed in the first cycle as described in Section 9.1.

In the Phase 2 part subjects will receive the RP2D of eribulin mesylate IV on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle.

9.4.6 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days (90 days if given for SAEs and/or events of clinical interest [ECIs]) after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of, or interact with, eribulin mesylate or pembrolizumab may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) eribulin mesylate or pembrolizumab.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

Treatment with bisphosphonates and/or denosumab will be allowed for subjects with bone metastases.

9.4.6.1 Treatments for Pembrolizumab-Related Toxicities

Infusion Reactions:

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Subject may be premedicated 1.5h (±30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

9.4.6.2 Drug-Drug Interactions

Please refer to the investigator brochure (IB) for eribulin mesylate and the IB for pembrolizumab for the most current information.

No drug-drug interactions affecting eribulin mesylate are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when eribulin mesylate was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when eribulin mesylate was administered with or without rifampin (a CYP3A4 inducer). Eribulin me**sylate does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4** enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Eribulin mesylate is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes.

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

9.4.6.3 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies, such as chemotherapy, hormone therapy, or immunotherapy, this will be judged to represent evidence of disease recurrence or progression, and study drug will be discontinued. These subjects should complete all off-treatment assessments and continue to be followed for survival in the Posttreatment Phase.

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than eribulin mesylate and pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed

virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
    - Note: Inhaled steroids are allowed for management of asthma.

For subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor. Subjects may receive other medications that the investigator deems to be medically necessary

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9.4.7 Treatment Compliance

Both study drugs will be administered IV, and the site will keep a record for each subject during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.8 Drug Supplies and Accountability

Compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and the investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV

- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA). Unused study drugs that was shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drug and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drug to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drug that is to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drug may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drug is approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Pretreatment/Screening Assessments

Baseline characteristics and assessments will be collected during the Pretreatment Phase/Screening Period, which will last from -21 days to -1 day before the Treatment Phase begins. All Pretreatment and Screening assessments are listed in the Schedule of Procedures/Assessments (Table 8).

Medical/Surgical History and Physical Examination

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. Significant findings prior to the start of study drug will be recorded on the Medical History and Current Medical Conditions CRF.

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 8). A physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will be required only in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes during treatment from the screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Pregnancy Test

A serum (a 6-mL sample of blood will be collected) or urine beta-human chorionic gonadotropin (β-hCG) test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. Please refer to the Schedule of Procedures/Assessments (Table 8).

Electrocardiogram (ECG)

Electrocardiograms will be obtained at Screening as designated in the Schedule of Procedures/Assessments (Table 8). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a

minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.6.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

Other assessments

Additional Screening assessments will include safety laboratory assessments, vital signs, ECOG, mTNBC diagnosis, TNM staging at diagnosis (Appendix 8), prior anticancer therapy, and tumor tissue for PD-L1 expression.

9.5.1.3 Treatment/End of Treatment Assessments

Treatment and End of Treatment assessments are listed in the Schedule of Procedures/Assessments (Table 8).

Dose-limiting toxicity (DLT) assessments will be conducted for Phase 1b subjects. A DLT is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to either of the study drugs.

Hematologic Toxicities:

- Any Grade 4 thrombocytopenia or neutropenia lasting >7 days

Nonhematologic Toxicities:

- Episcleritis, uveitis, or iritis of Grade 2 or higher
- Any Grade 4 toxicity
- Any Grade 3 toxicity EXCLUDING:
    - Nausea/vomiting/diarrhea controlled by medical intervention within 72 hours
    - Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab
    - Transient Grade 3 AST or ALT elevation, defined as no more than 3 days with or without steroid use
- Discontinuation or delay of more than 2 weeks of either study medication due to treatment-related AE will be considered as a DLT

All subjects enrolled in Phase 1b will be assessed for DLTs during a DLT assessment window of the first cycle of 21 days. Subjects who discontinue study treatment prior to completing the DLT assessment window for any reason other than a DLT will be replaced.

End of Treatment assessments for all subjects will be collected within 30 days of the last dose of study drug. Subjects with SAEs and/or ECIs at the time of End of Treatment will be followed for 90 days after the last dose of study drug or, if the subject initiates new anticancer therapy, for 30 days following the last dose of study drug, whichever is earlier.

9.5.1.4 Efficacy Assessments

Tumor response data utilized in the main analysis of ORR, PFS and DOR will be obtained from an independent review of the imaging scans. In addition, these analyses will be performed using the investigators' determination of tumor response, which will be considered secondary. Detailed methodology for assessment by independent review will be provided in an Independent Imaging Review Charter. Secondary endpoint OS will be assessed throughout the study.

9.5.1.4.1 TUMOR RESPONSE ASSESSMENT

Tumor assessments will be performed using RECIST 1.1 (Appendix 3). Investigator assessment will be performed at each assessment time point and entered onto the CRFs. Copies of all tumor assessment scans will be sent to an independent core laboratory designated by the sponsor for efficacy assessment. Note: As of Protocol Amendment 05, tumor assessment scans will no longer be sent to an independent imaging core laboratory.

Tumor assessments will be carried out during the Pretreatment Phase and then every 9 weeks ± 1 week (or sooner if there is evidence of progressive disease) after the start of study treatment. Computed tomography/MRI scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/Day 1), at all tumor assessment time points, and as indicated clinically. Color photographs containing a mm scale must be taken of all skin lesions being used as target lesions. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable.

The CT scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated IV contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable. Ultrasound should not be used for radiographic tumor assessment. Chest disease may not be followed using chest x-ray.

A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at Screening (within 28 days prior to Cycle 1/Day 1), to assess potential CNS disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan will be performed at tumor assessment time points, if clinically indicated.

The tumor assessment schedule should not be affected by interruptions in study treatment.

The same method of assessment used at Screening must be used at all time points.

Throughout the study it is critical that the same imaging methodology be applied and contrast be consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

Bone scans will be performed at Screening, every 27 weeks, or sooner if clinically indicated, and at confirmation of CR. A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 27 weeks (within that 27th week) from C1D1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan will be required at confirmation of CR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

Tumor response will be confirmed by a second examination performed no less than 4 weeks after the first observation of response. Best overall response (BOR) of stable disease requires at least 1 posttreatment assessment that meets the SD criteria at least 8 weeks after the start of treatment.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks ± 1 week during Year 1, and every 9 to 12 weeks ± 1 week thereafter according to standard of care, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

9.5.1.4.2 irRECIST After Initial Radiologic Progression

Since pembrolizumab, like other immunotherapeutic agents, may produce antitumor effects after an initial increase in tumor burden, standard RECIST criteria may not provide a complete response assessment of its efficacy. irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by central imaging vendor review will be evaluated retrospectively.

The key changes for irRECIST from RECIST v1.1 is the ability to continue treatment, if clinically stable, until a repeat imaging scan ≥4 weeks after the first radiologic evidence of PD confirms progressive disease. Therefore, in addition to radiographic assessment of tumor response or progression, irRECIST (see Appendix 4) takes into account the clinical condition/stability of subjects (Table 6).

Clinically stable is defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor(s) at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Table 6 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the every 9 weeks (±1 week) imaging schedule

CR = complete response. N/A = not applicable, PD = progressive disease, PR = partial response, SD = stable disease.

- In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

- For a **clinically stable** subject with first radiologic evidence of progressive disease by RECIST 1.1 (ie, **unconfirmed progression of disease**), it is at the discretion of the

site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from study treatment. If radiologic progression is not confirmed by irRECIST per the site, then the subjects may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed at a later time point by the site.

  - **NOTE**: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in sections 6.0 Study Flowchart and be submitted to the central imaging vendor. Note: As of Protocol Amendment 05, tumor assessment scans will no longer be sent to the central imaging laboratory.

- Any subject deemed **clinically unstable** should be discontinued from study treatment at 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.
- In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks ± 1 week in Year 1, and every 9 to 12 weeks ± 1 week thereafter according to standard of care), until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

irRECIST data will be collected in the clinical database.

9.5.1.5 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

9.5.1.5.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for PK analysis on eribulin mesylate only. Time points for PK sample collections are as follows:

- For all Phase 1b subjects, PK samples will be collected on C1D1 at predose (0 hour), 15, 30 minutes and 1, 2, 4, 8, 24, 48, 72, 96, 120, and 144 hours after the infusion of study drug. These PK sample collection times may be adjusted for certain time points only for administrative reasons, and only with sponsor approval.
- For Phase 2 subjects, PK samples will be collected, if feasible, on C1D1 (at the end of the infusion, 0.5 to 6 hours and 24 to 120 hours after infusion) and on C1D8 (predose and at the end of the infusion).

Plasma concentrations of eribulin mesylate will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

9.5.1.5.2 PHARMACODYNAMIC ASSESSMENTS

Eribulin mesylate PK/PD analysis will be conducted to evaluate the relationship between exposure and efficacy and exposure and safety when eribulin mesylate is coadministered with pembrolizumab.

9.5.1.5.3 OTHER BIOMARKER ASSESSMENTS

Archived and/or fresh (if possible) tissue samples will be collected at screening for assessment of PD-1/PD-L1 expression. Fresh biopsy tissues should be limited to readily accessible tumor lesions (eg, breast, peripheral lymph node, or skin).

Collected tumor tissues may be used for potential assessment of mutations and other genetic alterations or genes that may be important in the development and progression of cancer as well as for potential use in diagnostic development. The decision to perform other biomarker assessments may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

9.5.1.6 Safety Assessments

Safety assessments will consist of the monitoring and recording of all AEs, including all CTCAE v4.03 grades for both increasing and decreasing severity (Appendix 6), and SAEs; regular monitoring of hematology, clinical chemistry, and urine; periodic measurement of vital signs; and the performance of physical examinations, as detailed in Table 8.

9.5.1.6.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are eribulin mesylate and pembrolizumab.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.

- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline).
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the Adverse Event CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF and for 30 days after the last dose of study treatment. SAEs will be collected for 90 days and ECIs will be collected for 30 days after the last dose or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. An AE will not be reported on the Adverse Event CRF if other anticancer treatment is started. All SAEs will be reported on the Adverse Event CRF.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine whether they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, or the start of new anticancer therapy, whichever comes first. SAEs must be followed for 90 days and ECIs for 30 days (see Section 9.5.1.6.2) after the last dose of study drug or, if the subject initiates new anticancer therapy, for 30 days following the last dose of study drug, whichever is earlier. However, treatment-emergent peripheral neuropathy of any grade will be followed until return to baseline or until another anticancer therapy is started, whichever occurs first. All SAEs should be followed to resolution or, if resolution is unlikely, to stabilization.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline), or:

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Events ([CTCAE v4.03]; see Appendix 6; also available from: http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.6.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.6.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 7. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 8) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Efforts should be made to conduct study visits on the day scheduled. However, the Cycle 1 Day 1 hematology and chemistry assessments may be performed within 3 days prior to the scheduled visit, while subsequent hematology or chemistry assessments may be performed within 24 hours prior to the scheduled visit. On all occasions when study drug administration is scheduled, all hematology, blood chemistry, and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug. Refer to Appendix 2 for the management of clinically significant laboratory abnormalities.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC
Clinical Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium, magnesium
Liver Function Tests	ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin
Renal Function	BUN, serum creatinine
Thyroid Function	TSH, T4[a]
Pregnancy	Serum β-hCG (if urine not done)
Other	LDH, total protein, glucose (fasting[b])
Urinalysis	Glucose, ketones, pH, protein, RBCs, WBCs, specific gravity
	Urine β-hCG (if serum not done)

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells.
a: Thyroid function will be assessed at the Screening Visit and then every 2 cycles (starting at C2) throughout the study. As of Protocol Amendment 05, TSH and T4 will be done at the discretion of the investigator.
b: Fasting glucose at Screen only.

Clinical laboratory tests during the study will be performed by trained staff at the study sites. Local laboratories will perform tests throughout the study. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.6.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.6.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 8) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person, if feasible.

9.5.1.6.5 Physical Examinations

Comprehensive and abbreviated physical examinations will be performed at the Screening Visit as previously described in Section 9.5.1.2 and throughout the study as designated in the Schedule of Procedures/Assessments (Table 8). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening

Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, and skin and a complete neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will be required only in the presence of clinical symptoms related to this region.

Abbreviated Physical Examination

Health status will be assessed by brief evaluation of the chest (including heart and lungs), abdomen, and limbs, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.6.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/ Assessments (Table 8). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. Electrocardiograms obtained at C1D1 and C1D8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.6) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.6.7 OTHER SAFETY ASSESSMENTS

Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, Day 1 of each treatment cycle, and at End of Treatment Visits. The table in Appendix 7 will be used to assess performance status.

9.5.2 Schedule of Procedures/Assessments

Refer to Table 8 for the description and timing of each procedure and assessment in the Pretreatment, Treatment, and Posttreatment Phases.

9.5.2.1 Schedule of Procedures/Assessments

Table 8 presents the schedule of procedures and assessments for the study.

Table 8 Schedule of Procedures/Assessments

Phase	Pretreatment	Treatment		Posttreatment	
Period	Screening	Treatment Cycle 1 Through Last Cycle (21-day cycle)		End of Treatment	Follow-up[o]
Day	Days -21 to -1	Day 1 (includes Baseline C1/D1)	Day 8	Within 30[a] days of final treatment	Every 12 weeks
Assessments					
Informed consent	X				
Inclusion and Exclusion Criteria	X				
Demographic[b]	X				
Medical/surgical history	X				
TNM Staging[c]	X				
mTNBC diagnosis	X				
Prior anticancer therapy	X				
Pregnancy test[d]	X				
PK[e]		X	X		
Tumor tissue for PD-L1 expression	X				
ECG[f]	X	X[f]	X[f]		
Hematology[g]	X	X	X	X	
Chemistry[h]	X	X		X	
TSH and free T4 levels[i]	X	X		X	
Urinalysis (dipstick)[j]	X	X		X	
ECOG	X	X		X	
Vital signs	X	X	X	X	
Physical examination[k]	X	X	X	X	
Eribulin mesylate[l]		X	X		
Pembrolizumab[m]		X			
Disposition				X	

Table 8 Schedule of Procedures/Assessments

Phase	Pretreatment	Treatment		Posttreatment	
Period	Screening	Treatment Cycle 1 Through Last Cycle (21-day cycle)		End of Treatment	Follow-up[o]
Day	Days -21 to -1	Day 1 (includes Baseline C1/D1)	Day 8	Within 30[a] days of final treatment	Every 12 weeks
Tumor assessments[n]	Throughout Study				X
Adverse events/SAEs	Throughout Study				X
Concomitant medications	Throughout Study				
Survival information[o]				X	

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, C1D1 = Cycle 1 Day 1, CT = computerized tomography, eCRF = electronic case report form, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, CR = complete response, irCR = immune-related Complete Response, IV = intravenous, PK = pharmacokinetic, SAE = serious adverse event, MRI = magnetic resonance imaging, RBC = red blood cells, TNM = tumor-node-metastases, TSH = thyroid stimulating hormone, T4 = thyroxine, WBC = white blood cell.

a: End of Treatment assessments for all subjects will be collected within 30 days of the last dose of study drug. Subjects with SAEs and/or ECIs at the time of End of Treatment will be followed for 90 days after the last dose of study drug or, if the subject initiates new anticancer therapy, for 30 days following the last dose of study drug, whichever is earlier. However, treatment-emergent peripheral neuropathy of any grade will be followed until resolution or until another anticancer therapy is started, whichever occurs first. All SAEs should be followed to resolution or, if resolution is unlikely, to stabilization.

b: Demography information includes date of birth (or age), sex, and race/ethnicity.

c: TNM staging at the time of diagnosis should be recorded in the eCRF.

d: A serum (6-mL blood sample will be collected) or urine β-hCG test will be performed at the Screening Visit for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. If a negative screening pregnancy test is obtained more than 72 hours before the planned first dose of pembrolizumab and eribulin mesylate, a separate serum or urine sample must be obtained and tested at the Baseline Visit assessment on C1D1.

e: Pharmacokinetic blood samples will be collected only for eribulin mesylate PK analysis. Time points for PK sample collections are as follows: For all Phase 1b subjects, PK samples will be collected on C1D1 at predose (0 hour), 15, 30 minutes and 1, 2, 4, 8, 24, 48, 72, 96, 120, and 144 hours after the study drug infusion. For Phase 2 subjects, PK samples will be collected, if feasible, on C1D1 (at the end of the infusion, 0.5 to 6 hours and 24 to 120 hours after study drug infusion) and on C1D8 (predose and at the end of the infusion).

f: Electrocardiogram (ECG) will be performed at Screening, C1D1, C1D8, and at any unscheduled visits as clinically indicated. ECGs obtained at C1D1 and C1D8 should be performed just prior to and immediately after receiving the eribulin mesylate infusion.

g: Hematology laboratory assessment must be reviewed prior to every eribulin mesylate administration. Cycle 1 Day 1 hematology assessments may be performed within 3 days prior to the scheduled visit. Subsequent hematology assessments may be performed within 24 hours before the scheduled visit.

h: Chemistry laboratory assessment must be reviewed prior to every pembrolizumab administration. Cycle 1 Day 1 chemistry assessments may be performed within 3 days prior to the scheduled visit. Subsequent chemistry assessments may be performed within 24 hours before the scheduled visit.

i: Assessment of TSH and free T4 levels are to be performed at the Screening Visit and then every 2 cycles (starting at Cycle 2) throughout the study. As of Protocol Amendment 05, TSH and T4 will be done at the discretion of the investigator.

j: Urinalysis will be assessed at the Screening Visit and on Day 1 at Cycles 2 and 4. Urinalysis will include glucose, ketones, pH, protein, WBCs, hemoglobin (or RBCs), and specific gravity. If urinalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.

k: Symptom-directed physical examination and abnormal clinically significant findings should be recorded on AE page of the CRF.

l: Eribulin mesylate will be given immediately following pembrolizumab on Day 1 (±3 day window is allowed) and alone on Day 8 (±2 day window is allowed) of a 3 week cycle.

m: Pembrolizumab will be given prior to eribulin mesylate, only on Day 1 of a 3-week cycle (±3 day window is allowed).

n: Screening tumor assessments using CT of the chest, abdomen, and pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast.

Treatment Phase: Tumor assessments of the chest, abdomen, and pelvis and other areas where scans were performed at screening or newly suspected disease should be performed every 9 weeks ±1 week after the start of study treatment (or sooner if there is evidence of progressive disease) and should use the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point).

Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast within 28 days prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves an irCR. For subjects with history of treated brain metastases, brain scans will be performed at tumor assessment time points if clinically indicated. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 27 weeks (within that 27th week) from C1D1, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, a bone scan will be required at confirmation of CR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks ± 1 week during Year 1, and every 9 to 12 weeks ± 1 week thereafter per standard of care, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

- As of Protocol Amendment 05, Follow-Up assessments in the Posttreatment Phase will not be performed after the subject completes the Off-Treatment visit assessments (or after the 90 day monitoring for subjects with SAEs and/or events of clinical interest).

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 8 for the Schedule of Procedures/ Assessments.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in oncology studies. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, pregnancy tests, radiologic studies, and assessment of AEs, are standard ICH GCP evaluations to ensure subject safety. The use of RECIST v1.1 for tumor assessment is widely accepted. See Appendix 3.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Serious adverse events and ECIs, regardless of causality assessment, must be collected through the last visit and for 90 days after the subject's last dose, or 30 days following the last doses if the subject initiates new anticancer therapy, whichever is earlier. All SAEs and/or ECIs must be followed to resolution or, if resolution is unlikely, until the event or sequelae stabilize. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure that all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by his/her institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Study Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events, Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study (all off-treatment study assessments should apply).

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Study drugs will be given IV by the study staff at the investigator site. No abuse or errors are anticipated.

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drugs outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose. For this study, an overdose of pembrolizumab will be defined as ≥1000 mg (5 times the 200 mg dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol.
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of the healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events/Events of Clinical Interest

Study-specific events (Events of Clinical Interest [ECIs]) should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

Events of clinical interest for this study include: an elevated AST or ALT lab value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2× ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an

additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

Discontinuation of study treatment does not represent withdrawal from the study.

A subject must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 8 cycles (24 weeks) with pembrolizumab and had at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab.

Note: The number of treatments is calculated starting with the first dose of pembrolizumab.

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the End of Treatment procedures indicated in the Schedule of Procedures/Assessments (Table 8).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate medical treatment and other

necessary measures for the subject. A subject who has stopped returning for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these reasons: AE(s), lost to follow-up, subject choice, (ie, subject chooses to discontinue from the treatment but is willing to participate in the Follow-Up portion of the study), progression of disease, withdrawal of consent (ie, subject no longer wishes to participate in the study and be contacted), pregnancy, sponsor discontinuation of the study, or other. Subjects will be judged as lost to follow-up only if they cannot be reached after 3 documented attempts (at least 1 week apart) by the site to contact them.

After the last subject has completed 35 cycles of pembrolizumab, all ongoing subjects will be transitioned off study. Subjects still receiving eribulin monotherapy at this time may continue to receive eribulin treatment off study through their pharmacy (if commercially available for that individual subject) or through a patient assistance program administered by the sponsor. Subjects will continue to receive eribulin investigational product and will be assessed according to the Schedule of Procedures/Assessments (Table 8) until they complete the End-of-Treatment visit, prior to their transition to commercial eribulin or an access program.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH

guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed by use of SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

RECIST 1.1 criteria will be used in the evaluation of tumor status for the primary, secondary and exploratory endpoints, irRECIST criteria will be used in the evaluation of tumor status for one of the exploratory endpoints. Tumor response data obtained per RECIST 1.1 by IIR will be utilized in the main analysis of ORR, PFS and DOR. In addition, tumor assessment data assessed per RECIST1.1 by investigator review and per irRECIST by IIR and investigator review will be considered as secondary or exploratory.

9.7.1.1.1 PRIMARY EFFICACY ENDPOINT

- Objective Response Rate (ORR) - defined as the proportion of subjects who had a BOR of CR or PR.

9.7.1.1.2 SECONDARY EFFICACY ENDPOINTS

- Progression-Free Survival (PFS) – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first
- Overall Survival (OS) – defined as the time from the date of first dose of study drug until date of death from any cause
- Duration of Response (DOR) – defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR.
- Clinical Benefit Rate (CBR) is defined as the proportion of subjects who had BOR of CR, PR, or durable stable disease (SD) (≥24 weeks)
- Estimates of ORR, PFS, OS, DOR and CBR in the PD-L1 Positive Set.

9.7.1.1.3 EXPLORATORY EFFICACY ENDPOINTS

- Time to Response (TTR) is defined as the time from the date of first dose of study drug to the first documented CR or PR for those subjects with a confirmed PR or CR.
- ORR, PFS, DOR, and CBR using irRECIST

All above endpoints based on tumor measurement will be assessed according to RECIST 1.1, unless otherwise specified.

9.7.1.2 Definitions of Analysis Sets

- The DLT Evaluable Set includes subjects who complete the first treatment cycle (ie, take at least 2 doses of eribulin mesylate with no more than 1 dose reduction and at least 1 dose of pembrolizumab) and have sufficient safety evaluation. Subjects who had a DLT event will be considered evaluable for the dose-limiting toxicity as well. It is the analysis set for DLT evaluation in the Phase 1b part.
- The Full Analysis Set (Safety Analysis Set) includes all subjects who received any amount of either study drug. This is the analysis set for safety analyses and analysis of PFS and OS.
- The Evaluable Analysis Set (subset of Full Analysis Set) includes all subjects who have both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early or death. It is the analysis set for efficacy analyses.

- The PD-L1 Positive Set (subset of Evaluable Analysis Set) includes evaluable subjects whose PD-L1 expression level is above the threshold that is to be specified prior to the final analysis. Key primary and secondary efficacy endpoints (ie, ORR, PFS, OS, and DOR) will be summarized in this analysis set.

9.7.1.3 Subject Disposition

The number and percentage of subjects who completed the study/discontinued from the study and reasons for discontinuation will be summarized.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Full Analysis Set, using descriptive statistics. Continuous variables include age, weight, vital signs, time since MBC diagnosis; categorical variables include sex, age group, race, disease stage (Appendix 8), ECOG-PS, bone, skin, liver, and lung metastases.

9.7.1.5 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days (90 days if given for SAEs and/or ECIs) after the subject's last dose. A listing of prior and concomitant medications will be included in the clinical study report of this protocol.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

At least 165 evaluable subjects on RP2D will be enrolled in the study, including Phases 1b and 2.

Bayesian predictive probability (PP) design was used in original study design. Under original design, in the combined Stratum 1 and 2 subjects, the ORR value per RECIST 1.1 by IRR was assumed to be 0.20 for the historical control based on the recent studies (Table 1). The ORR in this study is estimated to be 0.35. Under protocol amendment 1, approximately 100 evaluable subjects were expected to be enrolled. Bayesian PP was used to monitor the response rate after postbaseline tumor assessments of at least 38 subjects were available. The calculation of PP was based on the goal of claiming superiority of the combination at the end of the study if

$$P(p>0.2|data)\geq 0.95 \qquad (1)$$

where p was the response rate of the combination, 0.2 was the response rate of historical control based on single agents pembrolizumab and eribulin in recent studies (Table 1), 0.95 was the prespecified target probability (θ_T), and P(p>0.2|data) is the posterior probability. On the basis of the accumulated data thus far in the study, the probabilities of all possible future outcomes that lead to equation (1) at the end of the study would be added in order to obtain the predictive probability. Therefore, early decision of study termination prior to reaching approximately 100 evaluable subjects was possible for claiming the combination is promising when PP is above a prespecified upper threshold (θ_U) or for claiming futility when PP is below a prespecified lower threshold (θ_L). The upper and lower cutoff probabilities for decision-making, θ_U and θ_L, were set as 0.99 and 0.025. Under the predictive monitoring, the study proceeded as follows:

- If PP> θ_U(=0.99), stop the study and claim the combination promising
- If PP< θ_L(=0.025), stop the study and claim the combination not promising
- Otherwise, continue the study until the number of evaluable subjects reaches to 100

The Bayesian stopping boundaries are included in Appendix 1.

After completion of enrollment under protocol amendment 1, Bayesian PP is no longer used for continuous monitoring of efficacy and futility as the study will not be stopped early for either efficacy or futility.

Under protocol amendment 3, in Stratum 2 subjects, the hypotheses for ORR per RECIST by IIR are updated to be H_0: ORR=0.10 vs. Ha: ORR=0.25, based on the most recent pembrolizumab monotherapy study (Table 1). Therefore, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2 to provide >90% power for the comparison of H_0: ORR=0.10 vs. Ha: ORR=0.25 at 1-sided alpha value of 0.025. Under Protocol Amendment 4, additional subjects will be enrolled to ensure 100 evaluable subjects in Stratum 2 to obtain more precise estimate of ORR.

Final Analysis

In the evaluable subjects in Stratum 1 and 2 combined, Bayesian posterior probability in equation (1) will be evaluated to determine the efficacy of the combination regimen after the tumor response status has been collected from the last evaluable subjects. That is, to claim efficacy if P(p>0.2|data)≥0.95. A 2-sided 95% credible interval of objective response rate in the evaluable subjects will be constructed to aid the interpretation of the results. Details of predictive and posterior probabilities calculation will be provided in the SAP.

In the evaluable Stratum 2 subjects, a binomial exact test will be used to test the estimated ORR per RECIST 1.1 by IIR versus a historical response rate of 10% at 1-sided alpha value of 0.025.

Subjects in the Phase 1b part who were treated at the RP2D and were deemed evaluable will be combined with Phase 2 subjects in the efficacy analysis.

9.7.1.6.2 SECONDARY EFFICACY ANALYSIS

PFS, OS, and DOR

Progression-free survival (PFS), OS, and DOR will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS, OS, and DOR at 6 and 12 months will be presented with 2-sided 95% CIs if estimable. Censoring rules for PFS and DOR will be provided in the SAP.

The cumulative PFS, OS, and DOR will be plotted over time. The median, first, and third quartiles from Kaplan–Meier estimation for PFS, OS, and DOR will be provided with 95% CIs if estimable.

Clinical Benefit Rate

A 2-sided Clopper–Pearson 95% CI will be constructed for calculating exact binomial intervals.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSIS

The analysis of time to response (TTR) will follow the analysis of PFS. The analysis will be performed in the subjects with confirmed PR/CR by RECIST1.1.

In addition to RECIST1.1 by IIR, tumor assessment data (ie, ORR, PFS, DOR, and CBR) will be assessed per RECIST1.1 by investigator review and per irRECISTby IIR and investigator review in the sensitivity analysis.

All efficacy analyses will be performed in overall subjects and also for each stratum.

Efficacy outcomes will be further evaluated in the PD-L1 Positive Set. The clinical utility of PD-L1 as a predictive marker in mTNBC subjects who receive eribulin mesylate and pembrolizumab combination treatment will be assessed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic assessments of eribulin mesylate will be performed in all subjects in the Phase 1b part of the study. Subjects in the Phase 2 part will undergo sparse PK sampling for population PK/PD analysis where feasible.

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Plasma concentrations of eribulin mesylate will be analyzed to determine PK parameters including maximum plasma concentration (C_{max}), time to maximum plasma/serum

concentration (t_{max}), clearance (CL), area under the concentration-time curve (AUC), and terminal elimination phase half-life ($t_{½}$). These PK parameters will be calculated at a minimum and additional parameters will be calculated if the data allow. Further details on PK parameters will be included in the SAP.

Details of the PK analyses will be provided in a separate analysis plan.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Exploratory graphical analysis will be conducted for PK/PD evaluations and may be followed by model-based analysis.

Further details will be provided in a separate document.

9.7.1.7.3 PHARMACOGENOMIC AND OTHER BIOMARKER ANALYSES

Pharmacogenomic and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

9.7.1.8 Safety Analyses

Safety analyses will be performed for the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and ECGs. Safety will be summarized separately for subjects enrolled in Phase 1b and Phase 2 and combined, unless otherwise specified in the SAP.

RP2D and DLT

The Phase 1b study will include at least 1 safety run-in cohort in which 6 metastatic triple-negative breast cancer (mTNBC) subjects who receive eribulin mesylate 1.4 mg/m^2 on Days 1 and 8 and pembrolizumab 200 mg on Day 1 of a 21-day cycle (Dose Level 1). Subjects will be observed for dose-limiting toxicity (DLT) in the first cycle. The purpose of the safety run-in cohort(s) is to study safety of the 2-drug combination. The Phase 2 part will proceed with Dose Level 1 when no more than 1 subject has a DLT. Otherwise, a lower eribulin mesylate dose of 1.1 mg/m^2 and pembrolizumab 200 mg will be evaluated in another cohort of 6 subjects. If no more than 1 subject has a DLT in the first cycle, the Phase 2 part will proceed with Dose Level 0 as the RP2D. Otherwise, alternative doses (eribulin mesylate 0.7 mg/m^2) will be explored prior to the start of the Phase 2 part.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/duration on treatment, quantity of study treatment administered, dose intensity (ie, mg/m^2/week for eribulin mesylate) and the number of subjects requiring dose reductions, dose omission, and dose delay will be summarized for eribulin mesylate. The number of administrations of pembrolizumab will be summarized.

Relative dose intensity (RDI) for each study drug will be calculated as D_{ea}/D_{ep}, where D_{ea} is the actual total dose received and D_{ep} is the total planned dose. D_{ep} of eribulin mesylate is calculated based on a subject's body surface area (BSA).

The duration of exposure for each study drug in days is defined as the date of the last dose – the date of the first dose +1. Average cycle length is defined as the duration of exposure divided by the number of cycles in the study.

9.7.1.8.2 ADVERSE EVENTS

Dose-limiting toxicity in the first cycle will be used to determine the RP2D. The DLT rate will be summarized descriptively at each combination dose level in the DLT evaluable set. Subsequent dose-limiting toxicity will be reported and summarized as well.

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 17 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that had an onset date, or a worsening in severity from baseline (pretreatment), on or after the first dose of study drug administration up to 30 days (90 days for SAEs and/or ECIs) following study drug discontinuation.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by CTCAE v4.03.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to each study drug. Treatment-related TEAEs include those events considered by the investigator to be possibly or probably related to study treatment or with missing assessment of the causal relationship. Serious adverse events (SAEs), deaths, TEAE with Grade 3 or above, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Adverse events of clinical interest, described in Section 9.5.4.3.2, will be summarized descriptively. Details will be provided in the SAP.

9.7.1.8.3 LABORATORY VALUES

Clinical laboratory (ie, hematology, serum chemistry and qualitative urinalysis) values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference

(normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n[%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated.

Laboratory parameters that are graded in CTCAE (v4.03) will be summarized by CTCAE grade.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit.

9.7.1.8.5 ECOG PERFORMANCE STATUS

ECOG performance status will be summarized descriptively and by change from Baseline.

9.7.1.8.6 ELECTROCARDIOGRAMS

Electrocardiogram results will be evaluated on an individual basis by subject. Abnormal readings will be identified as those outside (above or below) the reference range. Electrocardiogram findings will be summarized.

9.7.2 Determination of Sample Size

A total of approximately 170 subjects (approximately 165 evaluable with at least 100 in Stratum 2) will be enrolled.

Under Protocol Amendment 1, 107 subjects including at least 6 from the Phase 1b part were enrolled in the study. Enrollment was into 2 strata, which included first-line (Stratum 1) versus second- and third-line (Stratum 2) subjects. Bayesian predictive probability was used to monitor the study after response data from the first 38 subjects were available. Sample size calculation was carried out assuming the historical response rate of 0.2. Using simulation, the model parameters (θ_L=0.025, θ_U =0.99, and θ_T=0.95) were calibrated such that the frequentist 1-sided Type I error was 0.0326 when the tumor response rate in the combination regimen was 0.2 (under frequentist's null hypothesis H_0), and the power was 0.9278 when the response rate was 0.35 (under frequentist's alternative hypothesis H_a). The expected numbers of subjects needed to reach the decisions were 56 and 61 when p=0.2 (under H_0) and 0.35 (under H_a), respectively. A vague beta prior distribution for response rate, p, was specified in PP calculation; that is, p~beta (0.2, 0.8). PP was updated for every 3 new subjects in the simulations, which mimics the group sequential decision making in a real study setting. Without Bayesian interim monitoring, the Type I error was estimated as 0.0358, and power was estimated as 0.9418 in demonstrating posterior probability $P(p>0.2|data) \geq 0.95$. Five thousand simulations were run to estimate these design characteristics.

Per Amendment 3, additional subjects will be enrolled to ensure 80 evaluable subjects in Stratum 2. Using binomial exact test, the power is 0.92 with 80 evaluable subjects to demonstrate statistical significance at 1-sided alpha of 0.025 for the assumptions of H_0: ORR=0.10 vs. Ha: ORR=0.25. With 80 subjects, the 95% confidence interval for ORR from binomial distribution will be 0.160-0.359 if the observed ORR is 0.25.

Per Amendment 4, additional subjects will be enrolled to ensure 100 evaluable subjects in Stratum 2. With 100 subjects, power will be increased to 98% and the 95% confidence interval for ORR from binomial distribution will be 0.169-0.347 if the observed ORR is 0.25.

9.7.3 Interim Analysis

Under Protocol Amendment 1, interim decisions could be made on the basis of the expected response rate at the end of the study, which compromises the current information with the future sample size via a predictive probability approach. The Bayesian design can continuously update the predictive probability of the study outcome, such that early termination of a study is possible for either superiority or futility. The prespecified Bayesian stopping boundaries are included in Appendix 1. One interim analysis was performed after the first 39 enrolled subjects completed at least 2 tumor assessments or discontinued due to PD or death.

9.7.4 Other Statistical/Analytical Issues

Primary, secondary, and exploratory endpoints ORR, PFS, DOR, and CBR will be summarized in the evaluable analysis set in which an evaluable baseline tumor assessment and at least 1 evaluable postbaseline tumor assessment are required. In the analyses described above and any other sensitivity analysis, subjects with missing data will be considered as nonresponders in ORR and CBR calculation and nonresponders will be excluded in the analysis of DOR.

Any other statistical/analytical issues will be discussed in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

The SAP will be finalized prior to the database lock in this exploratory study. Any deviation from analysis plan described in the protocol will be documented in the SAP.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and the IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator or designee will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays and other imaging reports, (eg, PET/CT scans, magnetic resonance images, ECGs) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Study treatment compliance (eg, the reason for dose increase/reduction)
- Discontinuation information
- Sampling date and time for the drug concentration
- Sampling date and time for the clinical laboratory test

- Comments and other information on AEs (eg, severity, relationship to study treatment, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that the investigator contact the sponsor at the completion of the required retention period, or should the investigator retire or relocate, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department must conduct audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission, pursuant to the terms and conditions set forth in the executed Clinical Study Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Bayesian Stopping Boundaries

N	LB	UB	N	LB	UB	N	LB	UB
38	6	16	60	12	22	82	19	27
39	6	16	61	12	22	83	19	27
40	6	17	62	12	23	84	19	27
41	7	17	63	13	23	85	20	27
42	7	17	64	13	23	86	20	27
43	7	18	65	13	23	87	20	28
44	7	18	66	14	23	88	21	28
45	8	18	67	14	24	89	21	28
46	8	18	68	14	24	90	22	28
47	8	19	69	14	24	91	22	28
48	9	19	70	15	24	92	22	28
49	9	19	71	15	25	93	23	28
50	9	20	72	15	25	94	23	28
51	9	20	73	16	25	95	24	28
52	10	20	74	16	25	96	24	28
53	10	20	75	16	25	97	25	28
54	10	21	76	17	26	98	25	28
55	10	21	77	17	26	99	26	28
56	11	21	78	17	26	100	27	28
57	11	21	79	18	26			
58	11	22	80	18	26			
59	12	22	81	18	27			

Appendix 2 Sponsor's Grading for Laboratory Values

The table below is an example of the Sponsor's Grading Laboratory Values based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). The study team should assess whether the sponsor's Grading for Laboratory Values is appropriate for individual studies. If this appendix is used, it is the study team's responsibility to ensure that the current version of the sponsor's Grading Laboratory Values is placed in the appendix.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/ LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low	<LLN – 8.0 mg/dL	<8.0 – 7.0 mg/dL	<7.0 – 6.0 mg/dL	<6.0 mg/dL

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
(hypocalcemia)	<LLN – 2.0 mmol/L	<2.0 – 1.75 mmol/L	<1.75 – 1.5 mmol/L	<1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 3 Overview of RECIST v1.1 for Evaluation of Tumors Response

Tumor response assessments in this clinical study will use RECIST v1.1 guidelines based on the article by Eisenhauer, et al., 2009, entitled "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)." This appendix contains an overview of the RECIST v1.1 guidelines. For complete details, the Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://www.ejcancer.com/article/S0959-8049(08)00873-3/abstract

Appendix 4 Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Investigators should follow the guidelines provided here, which are an adaptation of RECIST 1.1 and immune-related response criteria (irRC). The following guide represents a summary of irRECIST and is meant to help investigators in providing more objective and reproducible immune therapy-related tumor response assessments in solid tumors.

The key changes for irRECIST are:

- For this study, similar to that allowed for RECIST 1.1, irRECIST allows the site to select up to 5 target lesions at baseline, 2 per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions. The ability to continue treatment, if clinically stable, until repeat imaging scans ≥ 4 weeks later (in most cases at the next scanning time point) to confirm immune-related progressive disease (irPD)

irRECIST Lexicon	
1. Baseline Assessments	
Measurable (Target) Lesions	Measurable lesions must be accurately measured in at least 1 dimension with a minimum size of: • 10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis (SDi) for nodal lesions • 10 mm in LDi for clinical lesions (must be measured using electronic calipers) • Identify up to 5 lesions, not more than 2 from 1 organ system. Lymph nodes are considered 1 organ system • Likely to be reproducible across all time points • Representative of tumor burden • May include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation • Sum of diameters (SOD) of all target lesions including nodal and non-nodal are reported as baseline SOD which is used for assessing tumor response at follow-up time points
Bone Lesions	Regardless of the imaging modality, blastic bone lesions will **not be** selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.
Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the SOD of all target lesions at baseline. If other lesions with a nonliquid/nonnecrotic component are present, those should be preferred.
Lesions with Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (eg, previous irradiation, RF-ablation, TACE, surgery, etc). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progression in the lesion.
Nonmeasurable (Nontarget) Lesions	Non-target lesions will include: • Measurable lesions not selected as target lesions. There is no limit to the number of nontarget lesions that can be recorded at baseline • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases,

	leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc. • Multiple non target lesions from the same organ may be captured as a single item on the CRF (eg, multiple liver metastases) Non-target lesions should be reported as present at baseline
SOD $_{baseline}$	Sum of diameters at baseline = LDi of all non-nodal + SDi of all nodal target lesions
2. Time point Assessments after Baseline	
Target lesion measurements	Locate image that optimizes the LDi of the non-nodal target lesion or short axis of target node(s). There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate time point SOD (SOD $_{timepoint}$). Special consideration for target lesions: • If a target lesion is too small to measure, a default value of 5 mm should be entered on CRF. • If a target lesion is between 5-10 mm, actual diameter should be entered on the CRF. • If a target lesion splits into 2 or more lesion then the LDi of split lesions will be added and entered in place of that lesion. • If 2 target lesions merged to form 1 lesion, then the LDi of 1 should be entered as "0 mm" while the other lesion should have the diameter of the merged lesion.
Nontarget Lesion Assessment	Nontarget lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of nontarget lesions primarily contributes to the overall response assessments of irCR. Nontarget lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of nontarget lesions alone, even in the presence of stable disease or a PR in the target lesion is indicative of irPD. IrCR is not possible unless all nontarget lesions are absent.
Definition of New lesion	Any lesion which was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment must be used by the PI • May include a lesion in an anatomical location that was not scanned at baseline (ie, brain) • Should be unequivocal and not due to differences in scanning technique • If equivocal, should be assessed at next time point; if present, irPD is the date the lesion was first seen (not the date confirmed)
3. irRECIST Overall Tumor Assessment	
irCR	• Complete disappearance of all measurable and nonmeasurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed irCR). • Lymph nodes must decrease to <10 mm in short axis. • Confirmation of response is required ≥ 4 weeks later, preferably at next time point, to be considered a confirmed irCR.
irPR	• If the **SOD$_{timepoint}$ of TLs decreases by ≥30 % compared to SOD$_{baseline}$** and there are no unequivocal new lesions, and no progression of nontarget disease, it is an irPR (unconfirmed). • Confirmation is required ≥ 4 weeks later, preferably at next time point, to be considered a confirmed irPR.
irSD	Failure to meet criteria for irCR or irPR in the absence of irPD. • If the sum of the TLs and the status of the nontarget lesions do not reach the criteria to meet irPR or irPD (an increase of ≥20% and at least 5 mm absolute increase in SOD compared to nadir†), the response is irSD.

<table>
<tr><td></td><td>

irSD = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir.
†SOD_{nadir}: Lowest measure SOD of TLs at any time point from baseline onward.

</td></tr>
<tr><td>irPD</td><td>
A minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or irPD for nontarget lesion(s) or unequivocal new lesion(s).

Confirmation of progression is recommended at a minimum of 4 weeks after the first irPD assessment (preferably at the next tumor assessment time point).

The decision to continue study treatment after the first evidence of PD is at the investigator’s discretion based on the clinical status of the subject as described in table below:
<table>
<tr><td></td><td colspan="2">Clinically Stable</td><td colspan="2">Clinically Unstable</td></tr>
<tr><td></td><td>Imaging</td><td>Treatment</td><td>Imaging</td><td>Treatment</td></tr>
<tr><td>1st radiologic evidence of PD by RECIST 1.1</td><td>Repeat imaging at ≥4 weeks (next TA time point) to confirm PD</td><td>May continue study treatment at the local site investigator’s discretion while awaiting confirmatory tumor imaging by site by irRECIST</td><td>Repeat imaging at ≥4 weeks to confirm PD per physician discretion only</td><td>Discontinue treatment</td></tr>
<tr><td>Subsequent tumor imaging confirms PD by irRECIST at the local site</td><td>No additional imaging required</td><td>Discontinue treatment (exception is possible upon consultation with sponsor)</td><td>No additional imaging required</td><td>N/A</td></tr>
<tr><td>Subsequent tumor imaging shows SD, PR, or CR by irRECIST at the local site</td><td>Continue regularly scheduled imaging assessments</td><td>Continue study treatment at the Investigator’s discretion</td><td>Continue regularly scheduled imaging assessments</td><td>May restart study treatment if condition has improved and/or clinically stable per investigator’s discretion. Next tumor image should occur according to the every 9 weeks ± 1 week) imaging schedule</td></tr>
</table>
Subjects may continue receiving study treatment while waiting for confirmation of
</td></tr>
</table>

	irPD if they are clinically stable as defined by the following criteria: • Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression • No decline in ECOG performance status • Absence of rapid progression of disease • Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact the sponsor to discuss continuing treatment.
irNE	Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure.

In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

• For a clinically stable subject with first radiologic evidence of progressive disease by RECIST 1.1 (ie, unconfirmed progression of disease), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from study treatment. If radiologic progression is not confirmed by irRECIST per the site, then the subjects may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed at a later timepoint by the site.

o NOTE: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in sections 6.0 Study Flowchart and be submitted to the central imaging vendor. Note: As of Protocol Amendment 05, tumor assessment scans will no longer be sent to the central imaging laboratory.

• Any subject deemed clinically unstable should be discontinued from study treatment at 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

• In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks ± 1 week in Year 1, and every 9 to 12 weeks ± 1 week thereafter according to standard of care), until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

Derivation of irRECIST overall responses			
Measurable response	**Nonmeasureable response**		
Target Lesions (% change in SOD)*	**Nontarget Lesions Status**	**New Lesions Status**	**Overall Response (irRECIST)**
↓100	Absent	Absent	irCR¥
↓100	Present/NE	Absent	irPR¥
↓≥30	Present/Absent/NE	Absent	irPR¥
↓<30 to <20↑	Present/Absent/NE	Absent	irSD
↓100 ↓≥30 ↓<30 to <20↑ NE	Present/Absent/NE	Present	irPD¥
↓100 ↓≥30 ↓<30 to <20↑ NE	Unequivocal progression	Any	irPD¥
↑≥20 from nadir	Any	Any	irPD¥
NE	Present/Absent/NE	Absent	irNE¥

CR = complete response, CRF = case report form, ECOG = Eastern Cooperative Oncology Group, irCR = immune-related complete response, irNE = immune-related neuropathy, irPD = immune-related progressive disease, irSD = immune-related stable disease, N/A = not applicable, PD = progressive disease, SD = stable disease, SOD = sum of diameters, TA = tumor assessment, TL = target lesion.

***** Decreases assessed relative to baseline, including measureable lesions only.

¥ Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix 5 New York Heart Association Cardiac Disease Classification

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. On the basis of NYHA definitions, subjects are to be classified as follows:

Class	Definition
Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Adapted from The Criteria Committee of the New York Heart Association, 1994.

Appendix 6 Common Terminology for Adverse Events (version 4.03)

The National Cancer Institute's CTCAE v4.0 published 28 May 2009 (v4.03: June 14, 2010) provides descriptive terminology to be used for AE reporting in clinical studies. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 4.0 have be correlated with single-concept, MedDRA terms.

Grades in CTCAEs v4.03 refer to the severity of the AE. Grades of 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

ADL = Activities of Daily Living.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Cancer Therapy Evaluation Program, NCI CTCAE v4.0. Available from:

http://ctep.cancer.gov/protocolDevelopmentielectronic applications/docs/ctcaev 4.pdf

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com. CTCAE v4.0 is available online at: http://ctep.cancer.gov/protocoIDevelopmentielectronic applications/docs/ctcaev 4.pdf.

Appendix 7 ECOG Performance Status Scale

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

ECOG = Eastern Cooperative Oncology Group.

Adapted from Oken, et al., 1982.

Appendix 8 Breast Cancer TNM Staging System

Tumor (T), Node(N), Metastases (M)	
Stage	**Thickness/Characteristics**
T Classification	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ or Paget's disease of the nipple with no associated tumor
T1	Tumor ≤2.0 cm in greatest dimension
T1mic	Microinvasion of ≤0.1 cm in greatest dimension
T1a	Tumor >0.1 cm, but ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm, but ≤1.0 cm in greatest dimension
T1c	Tumor >1.0 cm, but ≤2.0 cm in greatest dimension
T2	Tumor >2.0 cm, but ≤5.0 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin
T4a	Tumor of any size with direct extension to chest wall
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both Ta and Tb
T4d	Inflammatory carcinoma[a]
Regional Lymph Nodes (N) Classification	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph nodes with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node involvement; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)

Tumor (T), Node(N), Metastases (M)	
Stage	**Thickness/Characteristics**
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
Pathologic (pN) Classification	
pNX	Regional lymph nodes cannot be assessed (not removed for pathologic study or previously removed)
pN0	No regional lymph node metastasis identified histologically
pN1	Micrometastases, or metastases in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1a	Metastases in 1 to 3 axillary lymph nodes (at least one >2.0 mm)
pN1b	Metastasis in internal mammary lymph nodes with micro- or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micro- or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4 to 9 axillary lymph nodes or in clinically detected and in internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in 10 or more axillary lymph nodes or in infraclavicular (level III axillary) lymph nodes or in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive level I, II axillary lymph nodes; or in >3 axillary lymph nodes and in internal mammary lymph nodes with micro- or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit >2.0 mm) or metastases to the infraclavicular (level III axillary) lymph nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes with micro- or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastases (M) Classification	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)

Clinical detection: as detected by imaging studies.

a: Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiographically there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is

due to tumor embolization of derrnal lymphatics with engagement of superficial capillaries.
Available from https://cancerstaging.org/references-tools/quickreferences/Pages/default.aspx

American Joint Committee on Cancer: Stage Groupings for Breast Cancer

Clinical Stage			
0	Tis	N0	M0
IA	T1, T1mic	N0	M0
IB	T0	N1mic	M0
	T1, T1mic	N1mic	M0
IIA	T0	N1	M0
	T1, T1mic	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1, T1mic	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
IIIB	T4	N0, N1, N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Available from https://cancerstaging.org/references-tools/quickreferences/Pages/default.aspx

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7389-M001-218

Study Protocol Title: An Open-Label Single-Arm Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination with Pembrolizumab in Subjects with Metastatic Triple-Negative Breast Cancer (mTNBC)

Investigational Product Name: E7389/eribulin mesylate and pembroluzimab

IND Number: 113851

SIGNATURES

Authors:

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7389-M001-218
Study Protocol Title:	ENHANCE 1: An Open-Label Single-Arm Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination with Pembrolizumab in Subjects with Metastatic Triple-Negative Breast Cancer (mTNBC)
Investigational Product Name:	E7389/eribulin mesylate/ pembrolizumab
IND Number:	113851

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date