LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 7

LCCC 1522: **:** Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #7 INCOPORATES (CHECK ALL THAT APPLY)

X Editorial, Administrative Changes
X Scientific Changes
X Therapy Changes
X Eligibility Changes

The purpose of this amendment is to update the eligibility criteria to reflect that liposomal cytarabine combined with daunorubicin (CPX-351) may be considered one of the allowed types of induction therapy for front-line AML that subjects must undergo prior to enrollment on this study. This change is the result of changes in standard of care AML therapy. Also, an echocardiogram is now required as a pre-study assessment.

Additional major changes to the protocol include: subjects will be allowed to receive 2 years of pembrolizumab therapy on this clinical trial as opposed of the before allowed 1 year of therapy, subjects will be allowed to undergo allogeneic stem cell infusion after greater than 21 days have elapsed as opposed to the previously mandated 30 days, an additional correlative objective will be assessed to determine the presence of minimal residual disease after pembrolizumab therapy and dose modification and supportive care guidelines for pembrolizumab will be based on the updated package insert recommendations.

Editorial, Administrative Changes

- Removal of UNCCN to change to LCCC CPO Multicenter/LCCC Multicenter
- Added in LCCC CPO Multicenter e-mail address throughout "(CPOMulticenter@med.unc.edu" as a source of contact
- Table 3- change formatting and changed title to "Dose Modifications"
- Section 6.8 assessment of safety was clarified to indicated that only subjects who receive pembrolizumab will be evaluable for safety assessments. Additional clarification was made to sections 2.4.2 and 4.6 to clarify removing subjects from study due to unacceptable AEs refers to the section of the study when subjects are receiving pembrolizumab therapy and not the induction therapy phase.

Scientific and Therapy Change

- Section 1.4.3- updated language to reflect updated IB dated 29June2018
- Section 1.7 – added correlative study goal #4 -"to assess for minimal residual disease after pembrolizumab.
- Section 3.1.5- added "liposomal cytarabine and daunorubicin (CPX-351)",
- Section 4.3 - Maintenance Phase- Updated –To reflect that the allogeneic stem cell infusion day 0 should occur now **> 21** days after the last infusion of pembrolizumab
- Section 4.10- updated to provide clarity by bulleted points
- Section 6.1- addition of screening echocardiogram as baseline prior to treatment. As a pre-study assessment for a baseline for standard of care monitoring given risk of fluid overload in patients with AML as well as risk of myocarditis with pembrolizumab.
  Section 6.2- add Transthoracic Echocardiogram as a part of the assessment
- Section 6.5- End of Treatment- Subjects are now to reach a 2 years of treatment
- Section 6.7.4 - added "Minimal Residual Disease Analysis" for clarity for Cryopreserved mononuclear cells from bone marrow aspirate and/or peripheral blood will be analyzed for minimal residual disease assays via flow cytometry, DNA or RNA PCR.
- Section 7.3.3- updated FDA Expedited Reporting requirements – to provide details on FDA safety reporting
- Section 9.2- add "Financial Disclosures" to required documents and removed (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance) as it is no longer needed.
- Section 9.5- added paragraph to add more detail on monitoring and source date queries
  Section 9.6.2 – Updated to language to refer Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.
- Section 9.6.3- added information on how deviation should be reported.
- Section 11.1 – Appendix A updated to reflect the updated IB for supportive care
- Section 11.2 –Appendix B updated to reflect updated IB AE

Eligibility Changes

- Section 3.1.5- Inclusion Criteria updated to include "liposomal cytarabine and daunorubicin (CPX-351)" as part of the induction therapy for front-line AML

The attached version dated June 2, 2018 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
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PROTOCOL AMENDMENT # 6

LCCC 1522: **:** Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #6 INCOPORATES (CHECK ALL THAT APPLY)

X Editorial
Scientific Changes
X Therapy Changes
Eligibility Changes

1) Section 4.2 Changed to clarify the inpatient duration to reflect institutional standards to discharge patients so that there is not a specific requirement to stay in the hospital until early recovery.
2) Section 4.2.1- changed the cytarabine administration to "approximately" 2 hours, per institutional guidelines
3) Section 6.1. Added footnote 13 to T&E calendar about three times weekly labs if patients discharged before early recovery
4) Section 6.1 Time and events table. Added buccal swab to be collected at screening. Those patients who did not have buccal swab collected at screening should have this sample collected at any time during follow up (clarified in footnote 12)
5) Sections: 6.2., 6.3.3, 6.4.1.1, 6.4.2.1: The following Section were updated to reflect the Thyroid function tests to be done: TSH, T3, and free T4.

The attached version dated November 1, 2017 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
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PROTOCOL AMENDMENT # 5

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #5 INCORPORATES (Check all that apply):

X Editorial
X Scientific Changes
Therapy Changes
Eligibility Changes

This protocol is amended to update definition of disease progression for PFS secondary endpoint based on revisions to AML Leukemia Net criteria in 2017. The protocol is revised to include adverse event management language provided in a Dear Investigator Letter issued on 10 February 2017 by Merck and Co., Inc. regarding cases of Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Immune-mediated myocarditis with pembrolizumab.

Editorial

1. Section 10 Reference #2 revised to include online reference to revised AML criteria in 2017.

Scientific

2. Updated sections 4.4.6 include supportive care guidelines for SJS, TEN and immune-mediated myocarditis.
3. Added SJS, TEN and myocarditis to adverse events associated with pembrolizumab in section 5.1.6
4. Updated section 6.9.1 to include revised definition of disease progression for PFS based on revisions to Leukemia Net criteria for AML in 2017
5. Thyroid Function tests are now required and no longer optional. Thyroid function will be monitored periodically during pembrolizumab maintenance therapy. The following sections were updated to reflect this change, Time and Events table in section 6.1 and footnote #10 to this table, and Sections 6.2, 6.3.3, 6.4.1 and 6.4.2

The attached version dated June 7, 2017 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
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PROTOCOL AMENDMENT # 4

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #4 INCORPORATES (Check all that apply):

X Editorial, Administrative Changes
X Scientific Changes
X Therapy Changes
X Eligibility Changes

Editorial, Administrative

1. Eligibility criterion 3.1.5 was subdivided for clarity
2. Study schema in section 4.1 revised to reflect up to 2 years of maintenance pembrolizumab (instead of 1 year)
3. Minor editorial changes made to Section 4.2
4. Edit to section 4.6 duration of therapy changed from 1 year to 2 years of maintenance therapy with pembrolizumab
5. Eliminated the need to obtain ECOG PS on Day 14 in the Time and Events table (section 6.1) and assessment section 6.3.3
6. Editorial revision required to have section heading 6.4.1 for Year 1 of maintenance and the corresponding assessments as 6.4.1.1 (Day1 of each cycle) and 6.4.1.2 (After every 6^{th} cycle) during year 1 of maintenance

Eligibility changes

1. Inclusion criterion 3.1.3 changed to ECOG PS = 0-1 (previously 0-2)

Therapy Changes

1. Increased duration of pembrolizumab maintenance therapy to 2 years (instead of 1 year) as noted in Time and Event table (section 6.1)
2. Added text to section 4.5.2 to allow for intrathecal chemotherapy on maintenance phase of the protocol as long as the subject is continuing to have a clinical response to treatment

Scientific Changes

1. Subjects receiving pembrolizumab maintenance therapy will be given the option to complete a quality of life (QOL) questionnaire. Assessment of QOL was added as an exploratory objective to section 2.3 and a corresponding endpoint was added to the section 2.4.3 Exploratory endpoints. The Promis Global Health QOL assessment has been added as Appendix 11.1 to the protocol. This assessment was also added to the Time and Events table in section 6.1, footnote #13 added to Tand E table related to this assessment. Mention of this optional assessment added to sections 6.4.1 and 6.4.2 which address maintenance therapy with pembrolizumab.

2. Exploratory Objective (2.3.3) and exploratory endpoint (2.4.3.2) were added to assess for MRD after Pembrolizumab therapy
3. Footnotes #11 and #12 to Time and Events table changed to collect additional biopsies and blood samples due to extension of maintenance therapy with pembrolizumab out to 2 years
4. Because duration of maintenance pembrolizumab extended to year 2, new treatment assessment visits added i.e., 6.4.2 Year 2 of Maintenance, section 6.4.2.1 (Day 1 of each cycle) and section 6.4.2.2 (After every 6^{th} cycle) during year 2.
5. Sections 4.2.1 and 4.2.2 modified regarding dose reductions of cytarabine due to organ dysfunction and allowance for administration of pembrolizumab in patients who have had dose reductions of cytarabine
6. Section 4.3 Maintenance section of protocol revised to allow for 2 years of maintenance pembrolizumab, thus bone marrow biopsies after every 4 (not 3) cycles of treatment (i.e., every 12 (not 9) weeks) for the first year, and then after every 6 cycles of treatment (i.e. every 18 weeks) during years 1-2. Plus up to 34 doses (not 17) of pembrolizumab may be administered.

The attached version dated March 17, 2017 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
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PROTOCOL AMENDMENT # 3

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #3 INCORPORATES (Check all that apply):

X Editorial, Administrative Changes
Scientific Changes
Therapy Changes
Eligibility Changes

1. A clarification was made to inclusion criterion 3.1.4 that recurrent AML will be defined by ≥5% myeloblasts in bone marrow aspirate and/or biopsy
2. Added Callie Coombs to list of Co-investigators
3. Modified section 9.4 registration procedures to allow for the UNC Site study coordinator to review/confirm eligibility and register patients without using the network (LCCC CPO Multicenter). This process only applies to the UNC Site. Affiliate sites must register patients through the LCCC CPO Multicenter)
4. Minor editorial clarifications were added to Section 4.2, Section 6.1 (Time and Events Table Headings) and to table footnotes 2, 5, 11 and 12. Sections 6.3.4 and 6.3.5 headings were aligned with headings revised in the Table of Assessments, and finally, a cross reference was corrected in Section 7.3.4.1.
5. Corrected the heading and a footnote in the Dose Modification Table for Pembrolizumab in Section 4.3.2

The attached version dated November 9, 2016 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
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PROTOCOL AMENDMENT # 2

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #2 INCORPORATES (Check all that apply):

X Editorial, Administrative Changes
X Scientific Changes
Therapy Changes
X Eligibility Changes

A summary of revisions is provided as follows:

1. Updated language on required contraception for male and female participants (inclusion criteria 3.1.19 and 3.1.2) + added Section 4.2.2.1 outlining definitions of adequate contraception.
2. Revised exclusion criterion 3.2.10.
3. Revised wording in Section 4.3.2 and Table 3 in this section.
4. Revised and simplified instructions in section 4.4.6 to align with MERCK provided protocol template language.
5. Updated overdose definition in Section 5.1.10.
6. Removed LDH from Serum Chemistries in sections 6.2-6.3. LDH only included in tumor lysis labs
7. Footnote 3 of T&E calendar, specified that pembrolizumab maintenance should be given every 21 days (instead of 3 weeks) +/- 3 days to accommodate clinic schedules and holidays. This change was noted in 6.4.1 as well.
8. Revised wording in 6.4.2 to make bone marrow biopsies LESS frequent ie, Bone marrow biopsy should be performed after treatment of every 4th cycle at least 1 day prior to the next treatment cycle.
9. Footnote 11of T&E calendar revised to indicate repeat biopsy after every 4 cycles of maintenance.
10. Updated language in 7.1.4 to include additional Merck definitions of reportable AEs
11. Revised Merck Reporting requirements in section (7.3.4) to align with MERCK provided protocol template language.
12. Section 7.3.4.1 Events of clinical interest (ECI) provides updated definitions/MERCK reporting requirements for ECI
13. Section 7.3.4.2 defines reportable pregnancy events and requirement for reporting these events to MERCK
14. Section 7.3.4.3 defines protocol-specific exceptions to SAE reporting
15. Typos corrected in Table in Section 8.2 outlining Pocock-stopping boundaries
16. Updated list of co-investigators on the title page of the protocol
17. Revised language around treatment for hyperphosphatemia in section 4.4.5

The attached version dated August 24, 2016 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
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UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 1

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

AMENDMENT #1 INCORPORATES (Check all that apply):

X Editorial, Administrative Changes
Scientific Changes
X Therapy Changes
X Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY

Editorial Administrative changes

Minor editorial changes made throughout:

- Removed Dr. Voorhees as Co-Investigator
- Requirement of collection of some tissue samples has been removed (section 6.7.4)

Eligibility

- On page 14 under Inclusion Criteria- 3.1.5- it should state the following: 'Must have received at least 1 cycle of induction therapy for front-line AML including cytarabine continuous infusion + anthracycline +/- cladribine or etoposide for 1 or 2 cycles.''
- cladribine in the above sentence which is a standard therapy that patients receive for front-line AML.
- On page 15 Eligibility 3.1.12 deleted

Samples

- Section 6.7.4 Minimal Residue disease assessment removed as these samples will not be shipped to MMS-NHLBI at NIH in Bethesda.
- Section 1.7 Correlative Studies

Objective # 6 removed since the minimal residue assessment will not be done at this point

The attached version dated August 24, 2016 incorporates the above revisions

LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

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Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: Merck, Inc.
Version: Amendment #7
Version Date: June 02, 2018

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LCCC 1522: Phase 2 Study of High Dose Cytarabine Followed by Pembrolizumab in Relapsed and Refractory Acute Myeloid Leukemia

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:

PI Signature: _____

Date: _____

Version Date: June 02, 2018

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is an open-label, single arm, multicenter phase 2 study of standard salvage high dose cytarabine (HiDAC) on days 1 through 5 followed by a single dose of the humanized monoclonal antibody targeted against cell surface receptor programmed cell death-1 (PD-1), pembrolizumab, on day 14 as induction therapy in patients with relapsed and refractory acute myeloid leukemia (AML). Patients who achieve at least a partial response (PR) post-induction will continue on pembrolizumab every 3 weeks for up to 1 year of maintenance therapy. We plan to enroll 37 patients in a Simon's two-stage design.

The hypothesis of this study is that HiDAC followed by pembrolizumab will be effective in relapsed and refractory AML with a combined complete remission (CR)/CR with incomplete recovery (CRi)) rate of ≥40%, superior to a historical control of 20%. We also hypothesize that the rate of unacceptable toxicity associated with HiDAC followed by pembrolizumab will not significantly exceed 20% (see section 2.4.2). Secondary endpoints include toxicity of this combination when used as induction, overall objective response rate (CR+CRi +PR) post-induction, toxicity of pembrolizumab maintenance in those patients with a response after induction, and progression-free survival (PFS), relapse-free survival (RFS) and overall survival (OS) in patients who receive maintenance pembrolizumab. We will also explore for an association between potential immune biomarkers and clinical outcomes with pembrolizumab. The overarching goals of these correlative studies are: 1) to identify and characterize mechanisms involved in T cell dysfunction in AML, 2) to identify potential predictive biomarker candidates to allow better selection of AML patients who may benefit from pembrolizumab, and 3) to identify new pathways that could be targeted to enhance the efficacy of pembrolizumab in AML.

1.2 Relapsed and Refractory AML

AML has an extremely poor prognosis with conventional chemotherapy agents. While approximately 70% of patients are expected to achieve a CR following intensive induction chemotherapy, the majority of these patients ultimately relapse and die of AML.[1] The European LeukemiaNet analyzed the 3-year relapse-free survival (RFS) rates of 1,550 patients treated on front-line Cancer and Leukemia Group B (CALGB) studies in AML between 1985 and 2006. Patients were stratified on this study based on cytogenetic and molecular risk factors into 4 risk groups: favorable, intermediate-1, intermediate-2 and adverse. The 3-year RFS rates were 55%, 23%, 34%, and 10% among younger (<60 years) patients in the favorable, intermediate-1, intermediate-2, and adverse risk groups, respectively. In comparison, older patients (≥60 years) had distinctively worse outcomes across each subset with 3-year RFS rates of 24%, 10%, 11%, and 6% among favorable, intermediate-1, intermediate-2, and adverse risk, respectively.[2]

Patients who do not respond to intensive induction chemotherapy (i.e., primary refractory disease) have an even worse outcome with an overall response rate of <20% with salvage chemotherapy agents.[3] Long-term survival in primary refractory AML patients is <5-10%.[4] In contrast, the overall outcome of patients with relapsed AML is dependent on multiple factors such as total duration of CR, age, performance status, cytogenetics/molecular markers, and previous allogeneic stem cell transplantation.[5] Based on these factors, Breems et al. stratified first relapse patients into 3 prognostic groups: favorable, intermediate and poor-risk. One-year overall survival (OS) was 70%, 49% and 16%, for favorable, intermediate, and poor-risk relapsed AML patients, respectively. [5]

Advanced age appears to be the most negative predictor of overall outcome in patients with relapsed AML. Rowe et al. reported in abstract form results from various Eastern Cooperative Oncology Group (ECOG) studies of 362 patients >55 years who initially achieved a CR with induction therapy. Sixty-five percent of these patients subsequently relapsed with a median overall survival (OS) <5 months and 5-year OS of 6% after disease relapse.[6,7]

The management of relapsed and refractory AML continues to be a major challenge. There is no accepted standard chemotherapeutic regimen for relapsed and refractory AML. A multitude of chemotherapeutic regimens exist but none of these regimens have consistently proven to be superior. High dose cytarabine (HiDAC) 3 gm/m^2 administered intravenously (IV) Q12hours for 12 doses is one commonly used treatment in this setting, and has been evaluated with and without the addition of anthracyclines in patients with relapsed and refractory AML. Data on this regimen are summarized in the next section.

1.3 Cytarabine

Cytarabine (cytosine arabinoside) is a nucleoside analog that incorporates into human DNA in the S phase of the cell cycle. Cytarabine is widely considered the most effective anti-leukemic chemotherapeutic agent in AML. HiDAC, with and without anthracyclines, has been evaluated in 78 relapsed and refractory AML patients (age range: 12-72 years). Thirty-four of these patients received HiDAC alone (3 gm/m^2 IV Q12hours days 1-6) and 44 patients received HiDAC (same dose and schedule) + daunorubicin 30 mg/m^2 IV days 7-9. The overall CR rates were similar between HiDAC and HiDAC + daunorubicin (44% vs. 59%, respectively; p=0.09). Median duration of response was only 5 months in both arms. In the HiDAC alone arm, there was a clear difference in CR rates between relapsed disease (CR rates = 63%) and primary refractory AML (CR rates = 20%).

In the HiDAC alone arm, all patients achieved bone marrow aplasia, and 91% of patients in both arms developed fevers. The percentage of patients with non-hematologic toxicities by organ system in the HiDAC alone arm were as follows:

eye (23% when eye drops were used; 76% when they were not); skin (32%), nausea and vomiting (88%), diarrhea (39%), and abnormal liver chemistries (79%). Moreover, 12% of patients had CNS toxicity with HiDAC alone, typically manifested as mild-moderate neurologic impairment, with 6% (n=2) experiencing Grade 3 CNS toxicity that resolved after treatment discontinuation.[8] For additional information regarding adverse events and possible risks of cytarabine, please see section 5.0.

Recent studies have suggested that cytarabine alone has response rates 15-20% in relapsed and refractory AML patients. A randomized phase III study compared vosaroxin + cytarabine versus cytarabine alone (1 gm/m^2 IV daily for 5 days) in relapsed and refractory AML patients. The CR rate for patients on the vosaroxin + cytarabine arm was 30% versus 16% in patients on the cytarabine only arm.[9] An international randomized phase III study of elacytarabine compared with physicians choice, which included high dose cytarabine, also showed CR rates of approximately 20% in the physician's choice arm. [10]Additionally, a randomized phase II study by ECOG recently compared three different promising regimens for relapsed and refractory AML: Arm A: carboplatin + topotecan, Arm B: flavopiridol + cytarabine + mitoxantrone (FLAM), Arm C: Sirolimus + Mitoxantrone + Etoposide + Cytarabine. FLAM was shown to be the most effective regimen in this trial, with a CR rate of 28%, while Arm A and Arm C produced CR rates of 14% and 15%, respectively.[11]

It is unclear whether 3 gm/m^2 of cytarabine is necessary and whether this dose is superior to 2 gm/m^2. Moreover, high doses of cytarabine (>2 gm/m^2) appear to increase the risk for cerebellar toxicity, especially in older patients and those with renal disease.[12] HiDAC at doses of 1-2 gm/m^2 has also been evaluated in combination with other chemotherapy agents in relapsed and refractory AML patients, such as topoisomerase inhibitors (mitoxantrone and etoposide),[3,13-15] fludarabine[16], cladribine[17,18], and clofarabine.[19,20] Response rates seen with these combinations range from 20-50% (median duration of response <9 months), with significant toxicities; 30-day mortality rates of these regimens range from 10-30%.

Given these data, there is a high unmet need to develop safe and effective novel therapeutic regimens for patients with refractory and relapsed AML. Investigational therapies are warranted in relapsed and refractory AML and are highly recommended over other conventional chemotherapy regimens.[21,22]

1.4 Pembrolizumab

Pembrolizumab (MK-3475) is a potent and highly selective IV humanized monoclonal antibody (mAb) of the immunoglobulin (Ig) G4/kappa isotype that directly blocks the interaction between Programmed Death-1 (PD-1) and its ligands, PD-L1 and PDL-2. This immune checkpoint blockade enhances functional activity of the target lymphocytes to facilitate an antitumor immune

response, leading to tumor regression and immune rejection of the tumor. Indications currently under investigation by the manufacturer of pembrolizumab include non-small cell lung cancer (NSCLC) and glioblastoma. Keytruda™ (Pembrolizumab) has recently been approved (at a dose of 2 mg/kg IV every 3 weeks) in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Further development of pembrolizumab in non-metastatic melanoma is ongoing. See section 5.1 and the latest pembrolizumab prescribing information and Investigator's Brochure for detailed information.

1.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[23] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[24-28] In particular, the presence of $CD8^+$ T-cells and the ratio of $CD8^+$ effector T-cells / $FoxP3^+$ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). [29,30] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, all of which are involved in the CD3 T-cell signaling cascade.[29,31-33] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[34] PD-1 is expressed on activated lymphocytes including peripheral $CD4^+$ and $CD8^+$ T-cells, B-cells, T regs and Natural Killer cells.[35,36] Expression has also been shown during thymic development on $CD4^-CD8^-$ (double negative) T-cells as well as subsets of macrophages and dendritic cells.[37]

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[37-40] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[34] Although healthy organs express little (if any) PD-L1, a variety of cancers are known to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[41] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.4.2 Preclinical Findings

In preclinical studies, T-lymphocyte responses in cells from healthy human subjects, patients with cancer, as well as in primates were strongly enhanced by pembrolizumab. The EC50 (i.e., concentration in which 50% of the maximum effect is seen) in human donor blood cells exposed to pembrolizumab has been reported to be between ~0.1 and 0.3 nM based on T-cell activation assays, and levels of cytokines, including but not limited to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα) and interferon gamma (IFN□) were changed by this antibody. Of note, pembrolizumab does not impact immune responses unless antigen is present. In syngeneic murine tumor models, an anti-murine PD-1 analog significantly inhibited tumor growth, and was synergistic with chemotherapy agents resulting in increased complete tumor regression rates.

Safety pharmacology/toxicology studies of pembrolizumab were conducted in cynomolgus monkeys and included both a 1-month and 6-month repeat dosing period study. The maximum dose administered in each was 200mg/kg, administered weekly in the 1-month study and every other week in the 6-month study. The antibody was well tolerated in both studies, with an increased incidence of inguinal swelling and increased splenic weights at the 200mg/kg dose the only notable findings in the 1-month study, neither of which was considered adverse. Anti-pembroliuzmab antibodies were detected in both studies, but not at the 200mg/kg dose. Further, based on the level of target engagement, the antibodies do not seem to impact pembrolizumab pharmacodynamics. The no observable adverse effect level (NOAEL) based on both studies is ≥200mg/kg/dose. See the most recent pembrolizumab Investigator's Brochure for additional details.

1.4.3 Clinical Findings

Pharmacokinetics and Dosing

Pharmacokinetic (PK) parameters were assessed during an open-label phase I trial of pembrolizumab (NCT01295827) that evaluated three dose levels of monotherapy in patients with advanced solid tumors (1mg/kg, 3mg/kg, and 10mg/kg every 2 weeks). No dose-limiting toxicities (DLTs) were observed and all three dose levels were well-tolerated. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels evaluated. No maximally tolerated dose (MTD) has been identified to date.

Two dose levels are being evaluated in several phase II or III trials in metastatic melanoma and NSCLC (2mg/kg and 10mg/kg every 3 weeks) (NCT01704287, NCT01905657) after initial data showed that every 2 week and 3 week dosing appeared equivalent. Based on these studies, it was determined that 2mg/kg and 10mg/kg dosing in melanoma had similar efficacy and safety with flat exposure-response relationships of pembrolizumab for efficacy and safety in the dose range of 2-10mg/kg q3weeks. In addition, there was no effect of tumor burden or disease indication on the distribution behavior of pembrolizumab as assessed by a population pharmacokinetic model. The half-life of pembrolizumab is estimated at 14-21 days.

A population pharmacokinetic (PK) analysis of pembrolizumab has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and supports both body weight normalized dosing or a fixed dose across all body weights (Merck, written communication).

The choice of the 200 mg every 3 weeks as an appropriate dose for the switch to fixed dosing of pembrolizumab (which is pending FDA approval, and which is incorporated into this study) is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks (the current FDA approved dose), 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe (Merck, written communication). The fixed dosing regimen will also reduce potential for dosing errors and reduce the complexity associated with weight-based dosing.

Clinical Safety

As of June 2017 pembrolizumab monotherapy and combination therapy have been administered to, 14,0444 subjects, with hematologic malignancies and solid tumors, in a total of 19 Phase I, II, and III clinical trials sponsored by Merck. Safety data are available for a total of 2799 subjects in 4 Merck-sponsored clinical trials. The majority of participants, 2727 or 97.4%, experienced 1 or more AE, and 2062 (73.7%) experienced 1 or more AE reported as drug-related by the investigator. Various dose-schedules, including 10mg/kg administered IV over 30 minutes every 2 weeks, have been studied. The most commonly reported treatment emergent adverse events (TEAEs) experienced in monotherapy trials are fatigue (37.3%), nausea (24.5%), decreased appetite (22.5%), cough (22.0%), pruritus (20.1%), dyspnea (19.1%), arthralgia (18.0%), diarrhea (22.3%) and rash (17.8%).

1.5 Rationale for Pembrolizumab in AML

Models of AML suggest that the PD-1 pathway is exploited by leukemic cells to evade immune surveillance.[42-48] Tumor progression in a murine AML model was associated with up-regulation of PD-1 on $CD8^+$ T cells and an increase in regulatory T cells (Tregs).[42] These experiments further demonstrated that PD-1 knockout mice had less leukemia burden and increased OS upon AML challenge compared to wild-type mice, despite the presence of a similar percentage of Tregs. Blockade of PD-L1, furthermore, led to an increase in proliferation of $CD8^+$ T cells specific for leukemic blasts and reduced leukemic burden.[42] Thus, the interaction between PD-1 and PD-L1 can facilitate Treg-induced suppression of $CD8^+$ effector T cells (Teff) and dampen the anti-tumor immune response. In primary leukemia samples, PD-L1 was shown to be up-regulated on AML blasts (including de novo expression), more so at relapse than at diagnosis, and was induced by inflammatory molecules, such as IFN- γ and TNF-α.[43,44] These data suggest that leukemia cells up-regulate expression of PD-L1 in the setting of inflammation, such as after receiving chemotherapy.

Up-regulation of PD-L1 and PD-L2 was also seen on leukemic cells after initial T-cell activation, which led to suppression of T helper response and cytokine production, with a resultant increase in Tregs. Blocking the PD-1 pathway on these leukemic cells with a PD-1-Ig fusion protein largely abolished this suppression. An intriguing phenomenon of "adaptive resistance" was seen in these experiments, whereby initial expression of co-stimulatory molecules on AML blasts, such as CD86 and ICOS ligand, led to specific T-cell expansion and activation. Leukemic cells in turn up-regulate PD-L1 and other co-inhibitory molecules and down-regulate co-stimulatory molecules in order to suppress subsequent T-cell activation.[46,47] This concept of adaptive resistance is also supported by data suggesting that the presence of co-stimulatory molecules such as CD-86 and ICOS ligand were associated with worse outcomes in AML, as T-cell activation eventually contributes to induction of immune escape mechanisms (i.e., PD-1/PD-L1 and CTLA-4).[48] Recently, Kronig et al.[45] demonstrated that

IFN- γ induced PD-L1 expression in AML patients in CR and relapse more so than at initial diagnosis. The increased PD-L1 expression observed in these patients was due to both up-regulation as well as de novo expression on previously PD-L1 negative precursor cells. These data further support the concept of adaptive resistance in AML, whereby tumor cells utilize the PD-1/PD-L1 pathway for tissue protection in light of an ongoing anti-tumor immune response.[45-48]

1.6 Rationale for HiDAC Salvage Chemotherapy Followed by Pembrolizumab

There is no accepted standard chemotherapeutic regimen for patients with relapsed or refractory AML. High doses of cytarabine (1-3 gm/m^2) have been shown to be effective in induction, consolidation, and the treatment of relapsed and refractory disease.[8,12,49] The MTD of cytarabine is 3 gm/m^2 administered every 12 hours for up to 12 doses.[8] However, 3 gm/m^2 increases the risk for cerebellar toxicities (as outlined earlier), conjunctival toxicities, and prolonged myelosuppression. Further, patients >60 years appear to have heightened toxicity with HiDAC with increased rates of cerebellar toxicity.[12] It is also unclear whether 3 gm/m^2 is superior to moderate doses (i.e., 1-2 gm/m^2) of cytarabine, the latter doses which have been investigated in combination with other chemotherapy agents. Based on these considerations, we plan to administer age-adjusted HiDAC (age <60 years: 2 gm/m^2 IV Q12hours days 1-5 for a total of 10 doses; age ≥60 years: 1.5 gm/m^2 IV Q12hours days 1-5 for a total of 10 doses) to minimize toxicities at the time of pembrolizumab administration on day 14. Investigational agents and regimens remain the priority in relapsed and refractory AML.[21,22] Chemotherapy is hypothesized to exacerbate immune exhaustion in tumor cells.[50] HiDAC provides an effective anti-leukemic cytotoxic effect, but response rates are low and not durable (see section 1.3). Pembrolizumab will be administered on day 14, 9 days after the completion of HiDAC chemotherapy, while patients are still aplastic.

The common toxicities of pembrolizumab outlined in section 1.4.3 do not overlap with the major toxicities of cytarabine, and the mechanism of action of each is unique. Therefore, we expect no more than additive toxicity. Further, pembrolizumab administration will not be given concomitantly with cytarabine, but on day 14, 9 days after cytarabine therapy is completed. Additionally, delaying pembrolizumab until day 14 should theoretically create a maximally exhausted immune state in leukemia cells due to “adaptive resistance” after chemotherapy (see section 1.5). Patients who achieve a response (i.e., PR/CR/CRi) to the induction phase will receive pembrolizumab 200 mg IV Q3weeks maintenance treatment to prevent or delay relapse from occurring by potentially creating a long-lasting anti-leukemic immune effect.

In this trial, toxicity will be monitored continuously, with sequential boundaries employed to suspend the trial if excessive toxicity is seen. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the Data and

Safety Monitoring Committee (DSMC) with a description of the toxicities and a rationale for why the study should be discontinued.

1.7 Correlative Studies

We will be conducting a comprehensive, multifaceted correlative approach to evaluate leukemic cells and host immune responses before and after pembrolizumab treatment. The overarching goals of these correlative studies are: 1) to identify and characterize mechanisms involved in T cell dysfunction in AML, 2) to identify potential predictive biomarker candidates to allow better selection of AML patients who may benefit from pembrolizumab, 3) to identify new pathways that could be targeted to enhance the efficacy of pembrolizumab in AML, and 4) to assess for minimal residual disease after pembrolizumab. To accomplish these goals, we will perform Multiplex next generation sequencing of DNA and RNA from tumor cells, comprehensive kinome analyses to seek predictors of pembrolizumab activity, epigenetic studies of T cells via ChIP sequencing, multi-color flow cytometric analyses of immune markers pre and post-pembrolizumab to determine markers of activity, and high-throughput DNA sequencing of T cell receptors IGH loci to determine T cell receptor repertoire and diversity in AML before and after pembrolizumab treatment.

We hypothesize that response to pembrolizumab will be associated with: 1) increased mRNA expression of PD-L1, 2) increased expression of general immune gene signatures associated with immune regulation, 3) clonal restriction in T-cell receptor (TCR) and B-cell receptor (BCR) repertoires, 4) increased tumor infiltration with effector cells of multiple lineages, 5) decreased tumor infiltration by regulatory cells of multiple lineages.

Some or all of these correlative studies may be conducted under the auspices of the UNC Master Biomarker Protocol for Pembrolizumab Studies (PI: Jonathan Serody, MD UNC), currently under final review for funding.

All patients will have pre- and post-treatment tumor tissue (i.e., bone marrow biopsies) as well as serial blood samples submitted for correlative studies to determine the dynamic nature of immune signatures pre and post-pembrolizumab.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Estimate the objective overall rate of CR (CR+CRi) for age-adjusted HiDAC (age <60 years: 2 gm/m^2 IV Q12hours days 1-5; age ≥60 years: 1.5 gm/m^2 IV Q12hours days 1-5) followed by pembrolizumab 200 mg IV on day 14 in relapsed and refractory AML patients

2.2 Secondary Objectives

2.2.1 Estimate the rate of unacceptable toxicity associated with HiDAC followed by pembrolizumab as induction therapy

2.2.2 Estimate the objective overall response rates (PR+CR+CRi) for HiDAC followed by pembrolizumab.

2.2.3 Characterize the toxicity associated with HiDAC followed by pembrolizumab as induction therapy

2.2.4 Characterize the toxicity associated with pembrolizumab 200 mg IV Q3weeks when used as monotherapy maintenance after an initial response to induction phase HiDAC followed by pembrolizumab

2.2.5 Estimate the relapse-free survival (RFS) and progression-free survival (PFS) of patients receiving maintenance pembrolizumab

2.2.6 Estimate the overall survival (OS) of patients who received induction phase treatment.

[redacted]

2.4 Endpoints

2.4.1 Primary Endpoint

The rate of CR+CRi as defined by the International European LeukemiaNet Guidelines in AML[21]

2.4.2 Secondary Endpoints

- The rate of unacceptable toxicity is defined as drug-related grade 3 non-hematologic toxicity (with exception of infusion reactions, rash, fever, infection, nausea, fatigue, and anorexia) persisting for >7 days with supportive care, or any drug-related non-hematologic grade ≥4 toxicity (excluding infection). Toxicity will be classified and graded according to National Cancer Institute's (NCI) Common Terminology Criteria for

Adverse Events (CTCAE, version 4.0). Any patient who receives pembrolizumab treatment on this protocol will be evaluable for toxicity.

- Clinician assessed toxicity of HiDAC followed by pembrolizumab, and toxicity of pembrolizumab maintenance monotherapy classified and graded according to NCI CTCAEv4
- PR+CR+CRi as determined by International European LeukemiaNet Guidelines in AML[21]
- RFS will be defined as time from day 1 of CR/CRi to relapse or death from any cause.
- PFS will be defined as time from day 1 of response (i.e., PR/CR/CRi) to progression or death from any cause.
- OS will be defined as time from day 1 of treatment until date of last known follow up or death of any cause.

[redacted]

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in this study:

3.1.1 Willing and able to provide written informed consent for the trial

3.1.2 ≥18 years and ≤70 years of age on day of signing informed consent

3.1.3 ECOG Performance Status 0-1

3.1.4 Have histologically or cytologically confirmed recurrent AML as defined by ≥5% myeloblasts in the bone marrow aspirate and/or biopsy

3.1.5 Must have received at least 1 cycle of induction therapy for front-line AML including:

- cytarabine continuous infusion + anthracycline +/- cladribine or etoposide for 1 or 2 cycles OR
- liposomal cytarabine and daunorubicin (CPX-351) OR
- high dose cytarabine with or without fludarabine OR
- cladribine or clofarabine OR
- ≥4 cycles of azacitidine/decitabine OR
- the equivalent experimental therapy (the latter as confirmed by the PI)

3.1.6 Cytoreduction allowed with hydroxyurea and/or leukapheresis for up to 14 days prior to D1 of treatment under LCCC1522. Patients must be off hydroxyurea for ≥12 hours prior to D1 of treatment under LCCC1522

3.1.7 Demonstrate adequate organ function as defined in the table below. All screening labs should performed within 14 days of D1 of treatment under LCCC1522.

System	Laboratory Value
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN unless due to Gilbert's Disease, hemolysis or leukemic infiltration **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants or patient has disseminated intravascular coagulation

Activated Partial Thromboplastin Time (aPTT)	deemed by investigator to be due to leukemia ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants or patient has disseminated intravascular coagulation deemed by investigator to be due to leukemia
[a]Creatinine clearance should be calculated per institutional standard.	

3.1.8 Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of HiDAC treatment and again prior to D1 of pembrolizumab treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.9 Female subjects of childbearing potential should be willing to use adequate method of contraception as outlined in Section 4.2.2.1 - Contraception for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. The two birth control methods can be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from the screening visit throughout the study period up to 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.10 Male subjects must agree to use an adequate method of contraception as outlined in section 4.2.2.1 – Contraception, starting with D1 of HiDAC through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.11 As determined by the enrolling physician or protocol designee, ability of the patient to understand and comply with study procedures

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

3.2.1 Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3.2.2 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose

of HiDAC treatment. **NOTE:** use of steroid eye drops starting at the time of HiDAC administration is allowed.

3.2.3 Has a known history of active TB (Bacillus Tuberculosis)

3.2.4 Hypersensitivity to pembrolizumab or any of its excipients

3.2.5 Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3.2.6 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.7 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer that has undergone potentially curative therapy.

3.2.8 Has known active central nervous system (CNS) leukemia; subjects with previously treated CNS disease may participate provided they are stable (without evidence of active disease by imaging for at least 4 weeks prior to the first dose of treatment, and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to D1 of treatment.

3.2.9 Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. 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.

3.2.10 Has evidence of interstitial lung disease or a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.2.11 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the

subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.2.12 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

3.2.13 Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment

3.2.14 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

3.2.15 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.2.16 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA qualitative is detected).

3.2.17 Has received a live vaccine within 30 days prior to the first dose of trial treatment
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

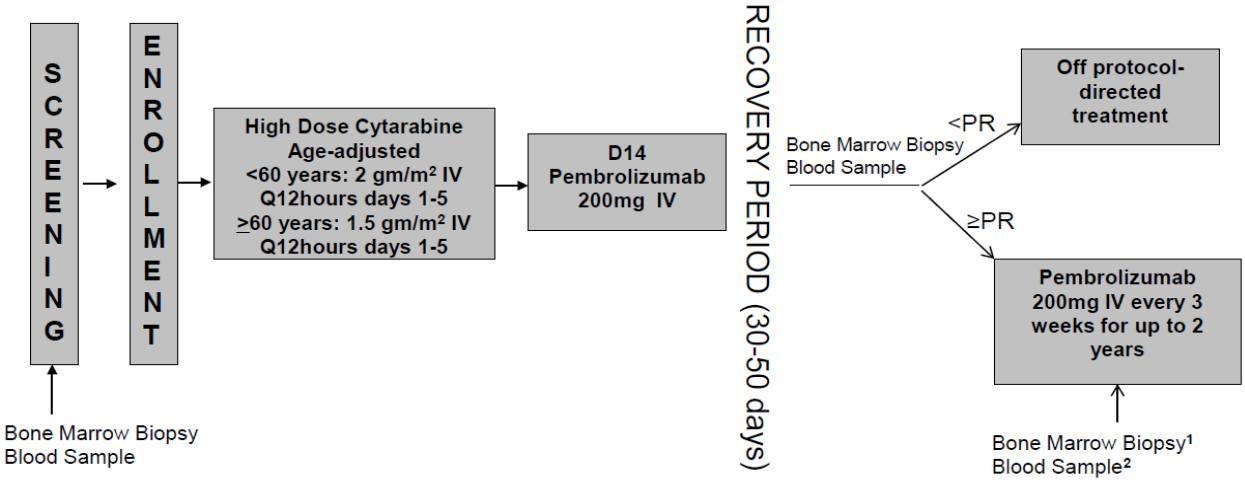
3.2.18 Has uncontrolled intercurrent illness including, but not limited to, active and uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, and uncontrolled symptomatic cardiac arrhythmia. Patients with infection under active treatment and controlled with antibiotics are eligible.

3.2.19 Diagnosed with acute promyelocytic leukemia (APL, M3)

3.2.20 Receipt of previous allogeneic stem cell transplant; receipt of previous autologous transplant for AML or non-AML condition is allowed

4.0 TREATMENT PLAN

4.1 Schema



[1]During Maintenance, bone marrow biopsy to be done after every 4th cycle of pembrolizumab for year 1, and every 8th cycle of pembrolizumab during years 1-2.
[2] See Time and Events Table for schedule of serial blood samples for correlative research

This is a phase 2, open-label, multicenter, single-arm study evaluating HiDAC salvage induction chemotherapy followed by pembrolizumab in the relapsed/refractory AML setting. Toxicity will be assessed during treatment via NCI CTCAE v4.0. Tumor specimens from a pre-study bone marrow biopsy and post-treatment bone marrow biopsies as well as serial blood samples will be collected for correlative studies.

Pembrolizumab 200 mg is administered IV once as monotherapy, 14 days after the initiation of HiDAC salvage induction chemotherapy. Patients who have a response (i.e., PR/CR/CRi) to induction phase will receive maintenance pembrolizumab at 200 mg IV every 3 weeks for up to 2-years of maintenance therapy (i.e., beginning on day 1 of maintenance).

4.2 Induction Phase

Treatment will be administered as an inpatient. Patients will be discharged from the inpatient unit after receiving pembrolizumab per institutional standards. All patients will receive standard high dose cytarabine (HiDAC) for salvage induction therapy dose-adjusted for age. Patients <60 years will receive HiDAC 2 gm/m^2 IV Q12hours days 1-5 while patients ≥60 years will receive HiDAC 1.5 gm/m^2 IV Q12hours days 1-5. Pembrolizumab will be administered as a fixed dose of 200 mg IV on day 14. Prior to pembrolizumab administration, patients must continue to meet eligibility for laboratory parameters as outlined in section 3.1. If

laboratory abnormalities exist on day 14, (or any patient with uncontrolled intercurrent illness or other abnormalities deemed by the PI to be unsafe to administer pembrolizumab), pembrolizumab administration can be delayed for 1 week, up to day 21, provided laboratory abnormalities correct themselves to levels defined in section 3.1 with supportive care. Patients who are ineligible for pembrolizumab administration by day 21 will be removed from the study and replaced by another subject. A disease assessment with a bone marrow biopsy will occur after patients have achieved full hematologic recovery as per standard of care, defined as absolute neutrophil count ≥1,000/mcL and platelet count ≥100,000/mcL. If full hematologic recovery does not occur by day 45 +/- 2 days, a bone marrow biopsy will take place regardless. Patients without evidence of active leukemia on disease assessment but without full hematologic recovery by day 45 +/-2 days will require a repeat bone marrow biopsy upon full hematologic recovery. Patients who achieve a CRi, will be followed with serial blood counts (weekly) for up to 30 days after bone marrow biopsy post-induction is performed. Those who achieve subsequent full hematologic recovery (within 30 days of CRi) will require an additional bone marrow biopsy to document full CR status. If they do not achieve full hematologic recovery within 30 days, they will remain designated as a CRi. Patients who have achieved a PR, CR or CRi will receive maintenance pembrolizumab (see section 4.3). Please see section 6.9 for response definitions.

REGIMEN DESCRIPTION				
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**
Cytarabine	Dexamethasone 0.1% ophthalmic eye drops 1 hour before cytarabine and Q6 hours both eyes days 1-12. See section 4.4.5 for prevention of tumor lysis syndrome	2 gm/m^2 Q12hours (1.5 gm/m^2 in ≥60 years)	IV over approximately 2 hours, per institutional guidelines	Days 1-5
Pembrolizumab	None	200 mg	IV over 30 minutes	Day 14

4.2.1 Cytarabine

Cytarabine will be administered on day 1, dose-adjusted for age (<60 years: 2 gm/m^2 IV Q12hours days 1-5; ≥60 years: 1.5 gm/m^2 IV Q12hours days 1-5). If organ dysfunction (i.e. renal dysfunction) arises during cytarabine administration, cytarabine can be dose-reduced after discussion with study team and PI. Cytarabine will be administered as an IV infusion over approximately 2 hours, per institutional guidelines. To prevent kerato-conjunctivitis, dexamethasone 0.1%

ophthalmic eye drops will be administered to both eyes Q6 hours at least 1 hour prior to cytarabine initiation and continued through day 12 of therapy (see Supportive Care).

Cerebellar exams should be performed prior to each dose of cytarabine. Any new symptoms suggestive of cerebellar toxicity should result in temporary discontinuation of cytarabine until symptoms resolve, as per institutional policy.

4.2.2 Pembrolizumab

All patients will receive pembrolizumab 200 mg IV for 1 dose on day 14 of therapy, as long as they have received >50% of planned doses of cytarabine (see 4.2.1). Pembrolizumab will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. This manual is provided as a document separate from the protocol.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Refer to the table below for infusion reaction 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 infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

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

4.2.2.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

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

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

OR

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

OR

(3) have a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal,

post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

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

4.3 Maintenance Phase

Patients who achieve a PR, CR, or CRi (see section 6.9) will receive pembrolizumab 200 mg IV Q3weeks on an outpatient basis. In order to qualify for pembrolizumab maintenance, all patients will be required to meet laboratory eligibility criteria as outlined in Section 3.1.7 and prior drug-related toxicities must have resolved to ≤grade 1 or baseline. Any patient experiencing unacceptable toxicity during induction, as defined in section 2.4.2, will not be eligible for maintenance, but will be discontinued from protocol-directed therapy and followed-up per protocol. In those who have achieved a CR or PR, pembrolizumab maintenance will begin 10-60 days following full hematologic recovery (absolute neutrophil count ≥1,000/mcL and platelet count ≥100,000/mcL). Patients who achieve CRi will begin maintenance pembrolizumab 10-60 days following a bone marrow biopsy disease assessment after induction phase (a repeat bone marrow biopsy should be performed if CRi patients subsequently achieve full hematologic recovery prior to pembrolizumab maintenance, as detailed in Section 4.2: Induction Phase). Patients eligible to receive maintenance therapy should begin maintenance as early as possible (≥10 days after hematologic recovery occurs, and once recovery from drug-related toxicities ≤grade 1 or baseline). Those who do not receive maintenance therapy by day 60 of hematologic recovery or by day 60 of post-induction bone marrow biopsy in CRi patients will be taken off study protocol.

All patients who continue pembrolizumab maintenance therapy will have disease assessments with bone marrow biopsies after every 4 cycles of treatment (i.e., every 12 weeks) for the first year, and then after every 6 cycles of treatment (i.e. every 18 weeks) during years 1-2. If there is suspicion for disease progression, a disease assessment via bone marrow biopsy will occur at any time during the maintenance phase. Patients will continue pembrolizumab 200 mg IV Q3weeks

for up to 2 years (i.e., 34 cycles of treatment) until disease progression, unacceptable toxicity, receipt of allogeneic stem cell transplantation or investigator and/or patient chooses to discontinue treatment.

Patients will be eligible to undergo an allogeneic stem cell transplantation after induction phase. Pembrolizumab maintenance can be continued prior to an allogeneic stem cell transplant. The allogeneic stem cell infusion day 0 should occur >21 days after the last infusion of pembrolizumab.

4.3.1 Toxicities and Dose Modifications for Pembrolizumab Maintenance

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See section 4.4 for supportive care guidelines, including use of corticosteroids.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). 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.

If a dose of pembrolizumab is delayed, then the subsequent dose should be administered 3 weeks later. Patients may receive up to 1 year of treatment with pembrolizumab beginning on day 1 of maintenance therapy. In the event of dose delays/interruptions, subjects may not receive more than 1 total year of treatment beginning with day 1 of maintenance therapy.

Table 3. Dose Modifications

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	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up

	(CTCAEv4.0)			
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants 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 participants 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). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to
	Grade 4	Permanently discontinue		

				drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be 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 participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants 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]		
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 and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants 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).

4.4 Rescue Medications & Supportive Care

4.4.1 Cytarabine-related Kerato-conjunctivitis

To prevent cytarabine-related kerato-conjunctivitis, dexamethasone 0.1% ophthalmic eye drops (or per institutional formulary) must begin at least 1 hour prior to cytarabine initiation. Eye drops should be performed every 6 hours to both eyes until day 12 of induction phase treatment.

4.4.2 Antiemetics

Antiemetics will be used according to standard practices with the exception of systemic steroids (i.e., dexamethasone). Use of systemic steroids during this trial is not allowed. Any 5-hydroxytryptamine (5-HT3) receptor inhibitor (e.g.,

ondansetron) combined with haloperidol or prochlorperazine as needed, will be used during chemotherapy infusions and during pembrolizumab administration, as needed.

4.4.3 Antimicrobial prophylaxis

Patients will receive prophylaxis against gram-negative gastrointestinal infections (GI), candidiasis, and herpes simplex virus (HSV), while patients are aplastic, during induction phase, and as per standard of care. Antimicrobial prophylaxis will only occur in the maintenance phase if patients develop neutropenia (absolute neutrophil count <500/mcL).

4.4.4 Colony Stimulating Factors

The routine use of colony stimulating factors is not allowed. The use of colony stimulating factors in the presence of severe or life-threatening infection should be discussed with the principal investigator before implementation.

4.4.5 Prevention and Management of Tumor Lysis Syndrome (TLS)

Tumor lysis occurs as part of initial cytoreductive therapy. In its most extreme form, TLS, is characterized by hyperuricemia, hyperphosphatemia, increased lactate dehydrogenase (LDH), coagulopathy, and a potential cytokine release syndrome.

Tumor lysis labs consisting of basic metabolic panel, uric acid, calcium, and phosphate must be drawn a minimum of twice daily at least through day 5 of chemotherapy and once daily through day 10, until maximum tumor lysis has abated. The following precautionary and prophylaxis regimens are suggested prior to and during initial chemotherapy administration:

- To prevent hyperuricemia, all patients without known allergy will receive allopurinol 300-600 mg PO qday 24 hours prior to beginning chemotherapy and the allopurinol 300-600 mg PO qday continuing through the period of maximal tumor lysis (at least through day 8) or other antiuricemia regimen per institutional practice. Rasburicase may be used per institutional policy for hyperuricemia. Screening for G6PD deficiency should be obtained in susceptible populations before beginning rasburicase.
- To decrease the risk of hyperphosphatemia, an oral phosphate binder per institutional practice (e.g. sevelamer 400-800 mg) will be administered orally every 8 hours beginning on day 1 of induction phase and continued as tolerated until maximum tumor lysis has occurred (at least day 8).
- Cytokine release syndrome can occur shortly after completion of drug infusion, accompany severe TLS, and present with fever, bronchospasm with dyspnea and/or respiratory distress, altered blood pressure, myalgias, arthralgias, tumor pain and/or urticarial rash. Any patient with cytokine release syndrome should receive 20 mg dexamethasone (or equivalent steroid) IV immediately. Pembrolizumab must begin at least 7 days after the last dose

of steroids for cytokine release syndrome.

4.4.6 Rescue Medications & Supportive Care for Pembrolizumab Cycles

Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined in below).

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

Pneumonitis:

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

Diarrhea/Colitis:
Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (TIDM) (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:
Thyroid disorders can occur at any time during treatment; monitor patients for changes in thyroid function (at the start of treatment, periodically during

treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 hyperthyroidism events (and **Grade 2-4** hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

Grade 3-4 hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Section 4.2.2 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

  Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

  - For signs and symptoms of SJS or TEN, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment
  - If SJS or TEN is confirmed, permanently discontinue pembrolizumab

Immune-mediated myocarditis management

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies and administer corticosteroids as appropriate

Infusion Reaction

See section 4.2.2.

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician

4.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

4.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase

- Anti-cancer systemic chemotherapy or biological therapy with the exception of hydroxyurea and intrathecal chemotherapy (cytarabine and/or methotrexate) for CNS disease. Intrathecal chemotherapy will be permissible on maintenance phase of the protocol as long as the subject is continuing to have a clinical response to treatment. This should be discussed with the PI prior to administering intrathecal chemotherapy. Intrathecal chemotherapy should be administered at least 72 hours before/after pembrolizumab infusion.
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic Corticosteroids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Radiation therapy
- Growth factor support (G-CSF or GM-CSF)

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

4.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Failure to achieve a PR, CR, or CRi after induction phase
- Disease progression/relapse at any time during induction or maintenance phase
- Receipt of allogeneic stem cell transplantation
- Completion of 2 years of pembrolizumab maintenance therapy
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) while on pembrolizumab therapy as defined in section 2.4.2
- Patient decides to withdraw from study
- Patient unable to comply with protocol requirements
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow-Up

Patients will be followed for up to 5 years after removal from study treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. After 2 years of follow-up as described in the time and events table, subsequent follow-up will be per standard of care and the study will follow only for progression and for survival for up to 3 additional years, for a total of 5 years of follow-up after study completion.

4.8 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.6 apply. Patients will also be removed from protocol therapy if they fail to meet eligibility criteria for the first dose of pembrolizumab following HiDAC induction (see section 4.2). The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.9 Patient Replacement

If laboratory abnormalities exist on day 14 during induction, pembrolizumab administration can be delayed for 1 week, up to day 21, provided laboratory abnormalities correct themselves to levels defined in section 3.1 with supportive care. Patients who are ineligible for pembrolizumab administration by day 21 will be removed from the study and replaced by another subject.

4.10 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

5.0 DRUG INFORMATION

5.1 Pembrolizumab

5.1.1 Description

Clinical Supplies will be provided by Merck as summarized in the table below.

Product Name & Potency	Dosage Form
pembrolizumab 50 mg	Lyophilized Powder for Injection
pembrolizumab 100 mg/ 4mL	Solution for Injection

5.1.2 Supplier/How Supplied

Pembrolizumab will be provided at no cost to the study patient by Merck, the manufacturer of the drug. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

5.1.3 Handling and Dispensing

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.1.4 Storage and Stability

See the Pharmacy Manual provided as a document separate from this protocol.

5.1.5 Return and Retention

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per UNC IDS drug destruction policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established

according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.1.6 Adverse Events Associated with Pembrolizumab

The most common adverse reactions (reported in ≥20% of patients in clinical trials of pembrolizumab) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

The following warnings are associated with the use of pembrolizumab:

Immune-Mediated Pneumonitis
Pneumonitis occurred in ~3% of melanoma patients treated in clinical trials of pembrolizumab. The median time to development of pneumonitis was 5 months with a median duration of 4.9 months. The one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred 1% of melanoma patients treated in clinical trials of pembrolizumab. The median time to onset of was 6.5 months with a median duration of 2.6 months. All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day).

Immune-Mediated Hepatitis
Hepatitis (including autoimmune hepatitis) occurred in 0.5% of melanoma patients treated in clinical trials of pembrolizumab. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Immune-Mediated Hypophysitis
Hypophysitis occurred in 0.5% of melanoma patients treated in clinical trials of pembrolizumab. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Renal Failure and Immune-Mediated Nephritis

Nephritis occurred in 3 (0.7%) patients of melanoma patients treated in clinical trials of pembrolizumab, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of pembrolizumab (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Immune-Mediated Hyperthyroidism
Hyperthyroidism occurred in 5 (1.2%) of 411 melanoma patients treated in clinical trials of pembrolizumab. The median time to onset was1.5 months and the median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Immune-Mediated Hypothyroidism
Hypothyroidism occurred in 34 (8.3%) of 411 melanoma patients treated in clinical trials of pembrolizumab. The median time to onset of hypothyroidism was 3.5 months. All but two of the patients with hypothyroidism were treated with long-term thyroidhormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism.Thyroid disorders can occur at any time during treatment.

Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with pembrolizumab, including exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

Across clinical studies with pembrolizumab in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

Embryofetal Toxicity
Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.

Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
The risk of SJS and TEN is reported at approximately 0.4 – 7 cases per million patient years in the general adult population. Independent risk factors include certain medications such as anticonvulsants, sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Non-medication triggers include infection, contrast media, and vaccinations. Malignancy is associated with an increased mortality rate in patients with SJS and TEN.

Myocarditis
A total of 6 cases of myocarditis have been reported in patients treated with pembrolizumab in clinical trials in an expanded access program. There was one fatal case reported in a clinical trial. Immune-mediated myocarditis should be suspected if other causes of myocarditis such as infection or prior radiation therapy have been excluded. Risk factors include certain medications and treatment modalities such as radiation, anthracycline, alkylating agents and most recently checkpoint inhibitors.

5.1.7 Contraindications

There are no reported contraindications associated with the use of pembrolizumab.

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

5.1.8 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the LCCC Multicenter Project Manager who will report the event to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the LCCC Multicenter Project Manager. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy

reported to the LCCC Multicenter Project Manager who will report the event to Merck, and followed as described above and in Section 7.3.3.

5.1.9 Use in Nursing Women

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

5.1.10 Overdose

For purposes of this trial, an overdose will be defined as any dose of 1,000 mg or greater (≥ 5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
All reports of overdose with and without an adverse event must be reported within 24 hours to the LCCC Multicenter Project Manager who will report the event within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) (see section 7.3.3).

5.2 Cytarabine

Mechanism of action: Cytarabine works by inhibition of DNA synthesis. Cytosine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytosine is a pyrimidine analog, which is incorporated into DNA; however, its primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair.

Product description: Cytarabine (conventional) is commercially available in vials containing 20 mg/ml (25 ml) and 100 mg/ml (20 ml) solution for injection and are stable at room temperature.

Solution preparation: Cytarabine can be compounded in 100-1000 ml of NS or D5W and is stable at room temperature for 48 hours once compounded. Cytarabine solutions reconstituted with diluents containing benzyl alcohol should not be used for intrathecal injections or for IV administration of high dose cytarabine (> 1

gm/m^2). Solutions for parenteral administration are generally reconstituted to concentrations ranging from 20-100 mg/ml, depending on the dose and the route of administration.

Solutions are stable at room temperature for 7 days, but use within 48 hours of preparation, or refrigerated for 24 hours beyond use date, is recommended by the manufacturer. Furthermore, solutions prepared with diluents which do not contain preservative or bacteriostat, should be used within 8 hrs of vial entry to minimize the risk of bacterial contamination.

Premedication: Dexamethasone 0.1% ophthalmic eye drops should be administered >1 hour prior to cytarabine infusion to both eyes and continued Q6hours through day 12 of treatment.

Route of administration: Cytarabine will be administered intravenously in a dose that adjusted due to age: <60 years: 2 gm/m^2 IV Q12hours days 1-5; ≥60 years: 1.5 gm/m^2 IV Q12hours days 1-5 over 2 hours. The infusion should not be interrupted for the delivery of blood products, antibiotics, etc.

Handling and Disposal: Please see policy on hazardous drugs:
http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf/view

5.3 Adverse Events Associated with Cytarabine

Serious and Common Adverse Effects:
The most common toxicities associated with cytarabine, even when used at doses ≤200mg/m^2 include hematologic (neutropenia, thrombocytopenia, anemia), gastrointestinal (nausea & vomiting (this agent is highly emetogenic), diarrhea and mucositis), dermatologic (rash), hepatic (hepatic dysfunction, mild jaundice, transaminase elevations), non-infectious fever, and alopecia. Additional toxicities associated with high dose cytarabine (≥ 1gm/m^2) include neurologic (primarily cerebellar such as nystagmus, ataxia, abnormal gait), but also cerebral such as somnolence, psychosis, confusion seizures), ocular toxicity, and rarely pulmonary edema.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessment	Treatment Schedule for Cycle 1 (INDUCTION)									RECOVERY PERIOD (30-45 DAYS)[2]	Full Heme Recovery or on D45 +/- 2 days[2]	For patients in ≥PR post recovery[3]	EOT[4]	Follow-up[5]
	Pre-study[1]	D1 Cycle 1	D2 Cycle 1	D3 Cycle 1	D4 Cycle 1	D5 Cycle 1	D 6-13 Cycle 1	D14 Cycle 1	Daily from D15 until early heme recovery or discharge from hospital[13]			D1 each cycle; continue cycles for 2 years of MAINTENANCE		
Informed Consent	X													
History[6]	X	X	X	X	X	X		X				X[6]	X[6]	X
Physical exam[6]	X	X						X			X	X	X	X
Performance Status	X	X										X	X	
Pregnancy Test[7]	X							X						
Echocardiogram	X													
CBC with differential	X	X	X	X	X	X	X	X	X		X	X	X	
Serum chemistries[8]	X	BID	BID	BID	BID	BID	X	X	X		X	X	X	
LDH, Uric acid, phosphate[8]	X	BID	BID	BID	BID	BID	X[8]	X						
Liver function tests[9]	X	X	X	X	X	X	X[9]	X	X[9]		X	X	X	
Coagulation labs[9]	X	X	X	X	X	X		X						
Thyroid function tests[10]	X							X				X		
Concomitant meds	X	X	X	X	X	X	X	X				X	X	
Toxicity Assessment		X	X	X	X	X	X	X	X		X	X	X[4]	X[3]
Bone marrow	X[11]										X[11]	X[11]		
Blood sample for biomarkers and buccal cell collection	X[12]							X[12]	Weekly[12]		X[12]	X[12]		
Cytarabine IV every 12 hours		X	X	X	X	X								

Pembrolizumab 200mg IV								X				X		
Survival analysis														X
QOL Questionnaire[14]												X		

Key to Time and Events Table Footnotes

[1] Unless otherwise noted, evaluations may be performed up to 2 weeks prior to Cycle 1 Day 1 of treatment. Cycle 1 Day 1 laboratory assessments do not need to be repeated if they have been performed up to 72 hours prior to the scheduled visit. **NOTE**: A window of 2 days will be applied to all study visits.

2Full hematologic recovery is defined as absolute neutrophil count ≥1,000/mcL and platelet count ≥100,000/mcL. All assessments listed including a disease assessment via bone marrow biopsy will occur at hematologic recovery, or by day 45 +/- 2 days, whichever comes first. See section 4.2 for additional details regarding D14 pembrolizumab delay.

[3]Patients in ≥PR based on BM biopsy may continue to receive pembrolizumab every 21 days +/-3 days (1 cycle) until maintenance treatment duration totals 1 year (see section 4.3 for additional details), disease progression, or intolerable toxicity, whichever occurs first. Pembrolizumab will start 10-60 days post full hematologic recovery in those who achieve PR or CR, and 10-60 days post the post induction bone marrow biopsy in those who achieve CRi. Patients who do not achieve at least a PR, or receive pembrolizumab maintenance by day 60 of hematologic recovery (or day 60 post-induction bone marrow biopsy in CRi patients) will be taken off of protocol-mandated therapy and followed up per protocol.

[4]This end of treatment (EOT) visit should occur in patients when they stop treatment whether due to disease progression, unmanageable toxicity, or they have reached 2years of treatment, and will take place ~30 days post last dose of pembrolizumab. Patients who experience ≥Grade 2 treatment-related adverse event will be contacted very 2 weeks until the event is resolved to Grade 0 or 1, determined to be irreversible by the investigator, or until the patient begins an alternate form of drug treatment.

[5]The first long-term follow-up visits will take place ~ 60 days after the EOT visit (+/- 15 days) and will focus on any serious adverse events (SAEs) or any grade of Events of Clinical Interest (see section7.3.4.1) that occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy). Any such events must be recorded. Subsequent long-term follow up visits will take place at a schedule as per institutional standard of care (i.e., usually every ~3-6 months) and will be limited to history of any subsequent cancer treatments, an assessment of any SAE's considered to be possibly or probably related to study treatment until resolution, and survival status.

[6]Complete history at baseline only, thereafter focused history on symptoms/toxicity. Physical exam to include height (baseline only), weight (D1 and D14 of cycle 1, D1 of all cycles of maintenance pembrolizumab and all follow-up visits) and vital signs

[7]Serum or urine B-HCG within 72 hours prior to D1 of HiDAC and prior to D14 pembrolizumab, and only if clinically appropriate; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[8]Serum chemistries include Na, K, Cl, creatinine, BUN, calcium, magnesium, bicarbonate,, and glucose; serum chemistries along with LDH, uric acid, and phosphate comprise tumor lysis labs. During induction, tumor lysis labs should be assessed BID (twice daily) D1-5, and once daily from D6 until tumor lysis syndrome is resolved, which usually occurs by D10. Repeat LDH, uric acid and phosphate on D14.

[9]Liver function tests (LFTs) include total protein, albumin, total bilirubin, alkaline phosphatase, ALT, and AST (**NOTE:** on D6-13, and on D15 through recovery, LFTs only required every other day); coagulation labs include PT/INR, aPTT, D-Dimer and fibrinogen

[10]Thyroid tests include T3, free T4, TSH as denoted during induction therapy. These tests should be performed on D1/C1 prior to starting maintenance therapy with pembrolizumab and repeated every 3 cycles thereafter (i.e., cycles 3, 6, 9, 12, etc.) until treatment discontinuation.

[11]Initial (pre-treatment) bone marrow biopsy should be obtained within 14 days prior to D1 of HiDAC as per standard of care. Patients will undergo repeat bone marrow at time of full hematologic recovery or on D45 +/- 2 days whichever comes first as per standard of care. Repeat biopsy after every 4 cycles of maintenance during year 1 and every 6 cycles of maintenance during year 1-2. Each time a bone marrow biopsy is done as per standard of care, additional 4x8mL will be collected in green top ACD tubes (~32 mL) for correlative studies. See section 6.7 and the laboratory manual for additional details. Repeat biopsy at any time if there is a suspicion of leukemia recurrence either during maintenance phase or in follow-up.

[12] Buccal cell collection should be collected from all patients during screening. If not done during screening, this can be performed at any point during follow-up. Please see laboratory manual for details. For peripheral blood samples for research, collect 5 x8mL ACD green top tubes of blood (~40mLs) pre-treatment within 14 days prior to D1 of HiDAC, D14 (1-12 hours prior to pembrolizumab administration), weekly between D14 and hematologic recovery (i.e. D21, D28, D35, and D42 (the latter if no full hematologic recovery by this time) and at full hematologic recovery or on D45+/- 2 days whichever occurs first. Repeat blood sample on D1 of each maintenance cycle of pembrolizumab during year 1 and every even cycle of maintenance during year 1-2. Repeat blood sample at any time if there is a suspicion of leukemia recurrence either during maintenance phase or in follow-up. See section 6.7 and the laboratory manual for additional details.

[13]Patients discharged from the hospital prior to early recovery should receive CBC, serum chemistries, and liver function tests at minimum three times weekly until early recovery

[14]Should be completed during each cycle of maintenance therapy (ie, day 1 of each cycle). Completion of the questionnaire will be optional.

6.2 Pre-Study Assessments

Clinical evaluation: complete history, physical examination to include height (baseline only) and weight, ECOG performance status.
Transthoracic Echocardiogram
Laboratory studies:

- **Pregnancy Test**: A serum or urine pregnancy test (β-HCG) is required for all women of childbearing potential at screening within 72 hours prior to the first dose of HiDAC. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- **CBC with differential and platelets**
- **Serum Chemistries:** These include the following parameters: sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, and magnesium.
- **LFTs:** These include total protein, albumin, total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)
- **Thyroid Function Tests:** TSH, T3, free T4
- **Coagulation Tests:** These include PT/INR, aPTT, D-Dimer and fibrinogen
- **LDH, Uric acid & phosphorus:** These along with serum chemistries and coagulation labs comprise tumor lysis labs

Concomitant Medications: Review (see section 4.4.6)
Tissue Acquisition/Disease Assessment: Primary tumor will be collected by peripheral blood and bone marrow biopsy. Buccal cell collection will be collected. Bone marrow biopsy and blood sample should be obtained within 14 days prior to day 1 of HiDAC. See section 6.7 and the laboratory manual for additional details.

6.3 Treatment Assessments-INDUCTION CYCLE (CYCLE 1)

6.3.1 Daily (or twice daily* as noted), D1-5 (High Dose Cytarabine administration)

Clinical evaluation: physical examination and ECOG performance status day 1 only, focused history on symptoms/toxicity days 1-5.
Laboratory studies:

- **CBC with differential and platelets**
- **Serum Chemistries*: twice daily:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium.
- **LFTs: total protein, albumin,** bilirubin (direct and indirect), alkaline phosphatase, AST, ALT
- **LDH, Uric acid, phosphate*: twice daily**
- **Coagulation Tests:** PT/INR/aPTT, D-Dimer, fibrinogen

Concomitant Medications: Review
Toxicity Assessment: via NCI CTCAEv4

6.3.2 Daily (unless otherwise noted) D6-13

Laboratory Studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium.
- **LDH, Uric acid, phosphate: NOTE,** once tumor lysis syndrome has resolved, these labs do not need to be repeated until D14
- **LFT's:** total protein, albumin, bilirubin (direct and indirect), alkaline phosphatase, AST, ALT: **NOTE**: **to be drawn every other day**

Concomitant Medications: Review
Toxicity Assessment: via NCI CTCAE V4

6.3.3 Day 14 (Day of Pembrolizumab infusion)

Clinical evaluation: focused history on symptoms/toxicity, physical examination to include weight.
Laboratory studies:

- **Pregnancy Test**: A serum or urine pregnancy test (β-HCG) is required for all women of childbearing potential prior to dose of pembrolizumab. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium.
- **LFTs: total protein, albumin,** total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)
- **Thyroid Function Tests:** TSH, T3, free T4
- **Coagulation Tests:** PT/INR, aPTT, D-Dimer, fibrinogen
- **LDH, Uric acid & phosphate:**

Concomitant Medications: Review (see section 4.4.6)
Toxicity Assessment: via NCI CTCAE v4
Blood sample for Biomarkers: Collect blood sample: see section 6.7 and the laboratory manual for additional details.

6.3.4 Daily (unless otherwise noted) Day 15 until Early Hematologic Recovery or Discharge from Hospital (see footnote #2 for definition)

Laboratory Studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium.
- **LFTs:** total protein, albumin, total bilirubin (direct and indirect), alkaline phosphatase, AST, ALT: **Note: To be drawn every other day**

Blood sample for biomarkers: Collect blood sample weekly between day 14 and hematologic recovery (i.e., day 21, day 28, day 35, day 42 (the latter 2 dates if no hematologic recovery by this time).

- Toxicity Assessment: via NCI CTCAEv4

6.3.5 At Full Hematologic Recovery or on Day 45 +/- 2 days (whichever comes first)

Clinical Evaluation: Physical exam including weight
Laboratory Studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium
- **LFTs:** Total protein, albumin, bilirubin (direct and indirect), alkaline phosphatase, AST, ALT

Toxicity Assessment: via NCI CTCAE v4
Disease Assessment and Biomarkers: Repeat bone marrow biopsy; collect blood sample for biomarkers; see section TBD and laboratory manual for additional details.

6.4 Treatment Assessments-Maintenance

6.4.1 Year 1 of Maintenance

6.4.1.1 Day 1 each Cycle

Clinical evaluation: focused history on symptoms/toxicity, physical examination to include weight, ECOG performance status.
Laboratory studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium
- **LFTs: total protein, albumin,** total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)
- **Thyroid Function Tests:** These include TSH, T3, free T4 (D1/C1 and then repeat every 3rd cycle (ie, cycles 3, 6, 9, etc)

Concomitant Medications: Review (see section 4.4.6)
Toxicity Assessment: via NCI CTCAE v4
Blood sample for Biomarkers: Collect blood sample, see section 6.7 and laboratory manual for details
Pembrolizumab administration: 200 mg IV, every 21 days +/- 3 days
Administer QOL Promis SF v1.1 –Global Health questionnaire (optional)

6.4.1.2 After every 4th cycle

Collect bone marrow biopsy for disease assessment and biomarkers: Bone marrow biopsy should be performed after treatment of every 4th cycle at least one day prior to the next treatment cycle; see section 6.7 and laboratory manual for details

6.4.2 Year 2 of Maintenance

6.4.2.1 Day 1 of each cycle

Clinical evaluation: focused history on symptoms/toxicity, physical examination to include weight, ECOG performance status.
Laboratory studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium
- **LFTs: total protein, albumin,** total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)
- **Thyroid Function Tests:** These include TSH, T3, free T4 (D1/C1 and then repeat every 3rd cycle (ie, cycles 3, 6, 9, etc)

Concomitant Medications: Review (see section 4.4.6)
Toxicity Assessment: via NCI CTCAE v4
Blood sample for Biomarkers: Collect blood samples every even cycle of treatment (i.e. every other cycle), see section 6.7 and laboratory manual for details
Pembrolizumab administration: 200 mg IV, every 21 days +/- 3 days
Administer QOL Promis SF v1.1 –Global Health questionnaire (optional)

6.4.2.2 After every 6th cycle

Collect bone marrow biopsy for disease assessment and biomarkers: Bone marrow biopsy should be performed after treatment of every 6th cycle (during years 1-2) at least one day prior to the next treatment cycle; see section 6.7 and laboratory manual for details.

6.5 End of Treatment

This visit should occur in patients when they stop treatment whether due to disease progression, unmanageable toxicity, or they have reached 2 years of treatment. In subjects who reach 2 full years of treatment, this visit will take place ~30 days post last dose of pembrolizumab.
Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, ECOG performance status.
Laboratory studies:

- **CBC with differential and platelets**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium
- **LFTs: total protein, albumin,** total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)

Concomitant Medications: Review (see section 4.4.6)
Toxicity Assessment: via NCI CTCAE v4; patients who experience ≥Grade 2 treatment-related adverse event will be contacted very 2 weeks until the event is

resolved to Grade 0 or 1, determined to be irreversible by the investigator, or until the patient begins an alternate form of drug treatment.

6.6 Follow-up

The first long-term follow-up visit will take place ~ 60 days after the EOT visit (+/- 15 days) and will focus on any serious adverse events (SAEs) or any grade of Events of Clinical Interest that occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy). Any such events must be recorded. Subsequent long-term follow up visits will take place as per institutional standard of care (i.e., typically every 3-6 months) and will be limited to history of any subsequent cancer treatments, an assessment of any SAE's considered to be possibly or probably related to study treatment until resolution, and survival status.

6.7 Correlative Studies Procedures

These are described in more detail in the laboratory manual. NOTE: A tumor sample will be sent to Merck or their designated laboratory for evaluation of PD-L1 expression at baseline. See laboratory manual for additional details.

Samples will be processed within 24 hours of collection as outlined in the Standard Operating Procedure Guidelines in the Laboratory Manual.

Some of the specific correlative details regarding specific antibodies, repertoires etc. may vary from this protocol, but will be maintained and updated in the corresponding laboratory manual.

6.7.1 mRNA Sequencing (mRNA-seq) and Proteonomics

mRNA-seq of bulk bone marrow leukocyte samples from diagnostic specimens will be performed for definition of tumor genetic subtypes, quantification of PD-L1 mRNA expression, and evaluation of gene expression signatures associated with immune activation and suppression. Bulk bone marrow leukocyte samples will also be sorted into $CD34^+$ and $CD34^-$ subpopulations, and the $CD34^+$ populations will undergo 1) mRNA-seq for neoantigen prediction and analysis of differential splicing, and 2) mass spectrometry for neoantigen confirmation. The $CD34^-$ fraction will be stored for the generation of cytotoxic T lymphocyte cultures for confirmation of biologically valid neoantigens.

The mRNA-seq studies will involve genetic research where tumor gene expression profiling and analysis of somatic mutations will be included. Appropriate informed consent for genetic research will be obtained prior to patient samples being processed.

6.7.2 High-Throughput DNA sequencing

Whole exome sequencing of $CD34^+$ AML blasts from bone marrow samples will be performed for somatic mutation detection and neoantigen prediction. From

bone marrow and peripheral blood leukocyte samples, T cell functional studies will be performed, and T cell receptor (TCR) and B cell receptor (BCR) repertoires will be amplified, sequenced, and analyzed to discover receptor profiles that correlate with response to therapy.

6.7.3 Flow Cytometry/Immunohistochemistry of Immune Markers

Bone marrow core biopsy blocks/slides may be stained for coexpression using the following panel of fluorescent antibodies (can include but not limited to): CD4/FoxP3, CD8/PD1, CD19/CD27, CD11b/CD33, CD47/CD68, along with immunohistochemistry staining using the following antibodies: PD-L1, IFN-γ, TNF-α, CTLA4, KIR3DL1, LAG3, CD200, Tim3 (HAVCR2), BTLA, CD137 (TNFRSF9), CD40, OX40, CD27, ICOS, and GITR (TNFRSF18), which combined will enable quantification and localization of effector T cells, regulatory T cells, myeloid derived suppressor cells, antigen-experienced vs. non-experienced B cells, and suppressive macrophages.

6.7.4 Minimal Residual Disease Analysis

Cryopreserved mononuclear cells from bone marrow aspirate and/or peripheral blood will be analyzed for minimal residual disease assays via flow cytometry, DNA or RNA PCR.

6.8 Assessment of Safety

Any patient who receives pembrolizumab treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (6.0). Toxicity will be assessed according to NCI CTCAE v4. Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab, all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document (provided as a document separate from this protocol) regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.0 for detailed information regarding the assessment and recording of AEs.

6.9 Assessment of Efficacy

Patients who have received pembrolizumab within the induction phase (cycle) will be evaluable for assessment of response and progression. Efficacy of treatment will be assessed by a bone marrow biopsy at the time of hematologic recovery (i.e., absolute neutrophil count ≥1,000/mcL and platelet count

≥100,000/mcL), or by day 45 +/- 2 days of induction treatment, whichever occurs first. Response will be assessed by standard international criteria proposed by the European LeukemiaNet Guidelines in AML.[21]

Complete remission (CR): Bone marrow blasts <5%; absence of Auer rods; absence of extramedullary disease; absolute neutrophil count ≥1,000/mcL; platelet count ≥100,000/mcL; independence of red cell transfusions

Complete remission with incomplete recovery (CRi): All CR criteria except for residual neutropenia (≤1,000/mcL) or thrombocytopenia (≤100,000/mcL) plus independent of platelet transfusions.

Partial response (PR): bone marrow blasts 5-25% and decrease of pretreatment bone marrow blast % by ≥50%; all hematologic criteria of CR.

Patients who achieve a PR to induction phase and then achieve CR after maintenance pembrolizumab will be assessed as an overall CR to study treatment.

6.9.1 Progression-Free Survival and Relapse

Progression-free survival (PFS) will be defined as time from response (i.e., PR/CR/CRi) until disease progression or death. In patients who achieve a PR after Induction Phase, progression will be defined as >50% increase in bone marrow blast % over baseline from beginning Maintenance Phase with a minimum 15% point increase in blasts, loss of PR (i.e., >25% bone marrow blasts), leukemia-related complications such as transfusion dependence, presence of extramedullary disease (including symptomatic CNS disease), or circulating blasts. This is consistent with European LeukemiaNet Guidelines 2017.[2] Progression will be defined as relapse (i.e., ≥5% bone marrow blasts) in patients who initially achieved a CR or CRi with induction phase. Patients who undergo an allogeneic stem cell transplant will be censored for PFS.

6.9.2 Relapse-Free Survival

Relapse-free survival (RFS) will be defined as time from CR or CRi until relapse or death. Relapse will be defined as bone marrow blasts ≥5% in a patient who initially achieved a CR or CRi after induction phase. Patients who undergo an allogeneic stem cell transplant will be censored for RFS.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a

drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered <u>unexpected if</u> the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs and Events of Clinical Interest

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 90 day follow-up period after treatment is discontinued (or to the initiation of new anti-cancer treatment, whichever is earliest).

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the LCCC Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the LCCC Multicenter using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancy or lactation

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy

of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, as a serious adverse event. The patient is to be discontinued immediately from any protocol directed therapy. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events. If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the LCCC Multicenter Project Manager who will report the event within 2 days to the manufacturer (Merck; see below 7.3.4.2).

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the LCCC Multicenter Project Manager within 24 hours via email (CPOMulticenter@med.unc.edu) or via facsimile to 919-966-4300. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

FDA Expedited Reporting requirements:
A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., “IND Safety Report,” and must be transmitted to the review division that has the responsibility for review of the IND. For this study, the review division is the Center for Drug Evaluation and Research. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the

suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing
FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up
The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators
The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process
If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to OnCore®) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form should be emailed or faxed to the Multicenter Project Manager at CPOMulticenter@med.unc.edu or 919-966-4300 along with supporting documentation defining the event and causality. The Multicenter Project Manager will then send the report to the Funding Source. The MedWatch 3500A form can be

accessed at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500A, and not form 3500).

Once the UNC Principal Investigator works with the sponsor to determine an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the Multicenter Project Manager will inform the Regulatory Associate at UNC, who with the aid of the IND Specialist, will submit the IND Safety Report via IND serial submission to the FDA review division.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

The Multicenter Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Additional Reporting Requirements
The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance
Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

7.3.4 Merck Reporting Requirements:

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

All subjects with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.3.4.1 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the LCCC Multicenter Project Manager who will report the event within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any

subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 5.1.10 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.4.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner) that occurs during the trial or within. Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/ randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days of completing the trial completing the trial following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All subjects and female partners of male subjects who become pregnant reported pregnancies must be followed to the completion/

termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.3.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported as AEs to Merck or FDA, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review

Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design and Sample Size

This is a multi-center prospective open-label single arm phase 2 study assessing the activity of age-adjusted HiDAC (<60 years: 2 gm/m^2 IV Q12hours days 1-5; ≥60 years: 1.5 gm/m^2 IV Q12hours days 1-5) salvage induction treatment followed by pembrolizumab 200 mg IV on day 14 for relapsed or refractory AML patients.

The subjects who achieve a response (CR, CRi, or PR) to induction phase HiDAC followed by pembrolizumab 200 mg IV on day 14, as assessed by standard international European LeukemiaNet Guidelines in AML,[21] will receive pembrolizumab 200 mg IV Q3weeks of maintenance therapy beginning 10-30 days following full hematologic recovery from induction phase. Maintenance treatment will continue until disease progression, toxicity, physician and/or patient discretion, or up to 1 year of treatment.

Simon's like two-stage design with relaxed stopping for futility will be used.[53] The null hypothesis that the true CR rate (CR/CRi) for HiDAC followed by pembrolizumab is 20% will be tested against a one-sided alternative hypothesis. In this study, "relaxed stopping" refers to inclusion of PR in the first stage as some of these PRs may convert to a CR during maintenance. In the first stage, 19 patients will be enrolled. If the number of patients who achieve a CR/CRi plus the number of patients with PR is equal to 4 or fewer in these 19 patients, the study will be stopped. Otherwise, 18 additional patients will be enrolled for a total of 37 patients. The null hypothesis will be rejected if 12 or more CR/CRi's are observed in 37 patients.. Assuming that the PR rate has a uniform distribution, Uniform (0, 0.05), under H_0, this design yields a type 1 error rate of at most 5% and power of at least 84% when the true CR rate for HiDAC followed by pembrolizumab is 0.4.

8.2 Continuous Monitoring for Toxicity

Sequential boundaries will be used to monitor unacceptable toxicity rate in the trial. An unacceptable toxicity is defined as any drug-related grade 3 non-hematologic toxicity (exceptions include infusion reactions, rash, fever, infection, nausea, fatigue and anorexia) persisting for >7 days despite supportive care), or any drug-related grade 4-5 non-hematologic toxicity (excluding infection). The accrual will be halted if excessive numbers of unacceptable toxicities is equal to

or exceeds b_n out of n patients with full follow-up (see Table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of unacceptable toxicity is equal to the acceptable rate of 0.2.

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	5	5	5	6	6	6	7	7	7	8	8	8	8	9	9
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37			
Boundary, b_n	9	10	10	10	11	11	11	11	12	12	12	13	13	13	13	14	14			

The stopping boundary above will guide enrollment as well as suspension of accrual (i.e., when to stop the trial if necessary). Initially 3 patients will be enrolled. Since the study is stopped when 3 unacceptable toxicities are observed in the first 3 patients, we will not enroll a new patient until at least one of the first 3 patients completes follow-up (i.e., reaches full hematologic recovery, deemed as refractory or CRi) and is confirmed not to have unacceptable toxicity. The enrollment will be continued in the same manner so that at any point in the trial the number of patients with unacceptable toxicities and the number of patients in the follow-up does not exceed b_n where n is the total number of patients accrued so far.

8.3 Data Analysis Plans

The primary endpoint of this study is the overall CR rate (CR+CRi) after HiDAC salvage followed by pembrolizumab on day 14. Responses will be assessed by standard international European LeukemiaNet Guidelines.[21]

Secondary endpoints include the following:

- Rates of unacceptable toxicity defined as any drug-related grade 3 non-hematologic toxicity (exceptions: fever, rash, infection, infusion reactions, nausea, fatigue and anorexia) lasting for >7days despite supportive care, or any drug-related grade ≥4 non-hematologic toxicity (excluding infection)
- Clinician assessed toxicity of HiDAC followed by pembrolizumab will be classified and graded according to NCI CTCAE, version 4.0.
- Objective overall response rates will be defined as PR+CR+CRi as determined by international European LeukemiaNet Guidelines in AML.[21]
- Clinician assessed toxicity of pembrolizumab maintenance will be classified and graded according to NCI CTCAE, version 4.0
- RFS will be defined as time from day 1 of CR/CRi to relapse or death from any cause.
- PFS will be defined as time from day 1 of response (i.e., PR/CR/CRi) to progression or death from any cause.
- OS will be defined as time from day 1 of treatment until date of last known follow up or death of any cause.

Survival distributions will be summarized using the method of Kaplan and Meier. We will report median time where possible. All demographic and analytic data will be summarized by descriptive statistics. Categorical data will be summarized using frequency tables while summary statistics such as means, medians, standard deviation, range, etc., will be provided for continuous data. 95% confidence intervals will be reported as well.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.

- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9.4 Registration Procedures

All patients at affiliate sites must be registered with the LCCC CPO Multicenter at the University of North Carolina before enrollment to study. To register a patient call the LCCC Multicenter at 919-966-7359 M-F 8:30am- 5pm EST. Securely scan and email the Multicenter Project Manager (preferred) or fax (919-966-4300) the registration form, signed informed consents, signed eligibility form and all source documents to confirm eligibility.

All UNC LCCC patients eligible for enrollment in this trial may be registered by the UNC site coordinator without using the network. The UNC site coordinator may review eligibility and register patients in the trial. This process only applies to the UNC site and not to external sites.

9.5 Data Management and Monitoring/Auditing

The CPO Multicenter of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). LCCC Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The LCCC Multicenter Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

All data will be monitored and source data will be verified on selected subjects. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt. The LCCC compliance committee or their designee will audit trial sites every twelve months while still enrolling or subjects are still on treatment. Participating sites must send source and regulatory documents to LCCC upon request, for remote monitoring and/or audit review.

9.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.6.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the LCCC Multicenter Regulatory Associate).

9.6.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

9.6.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be reported per the UNC IRB policies.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the LCCC Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the LCCC Multicenter Regulatory Associate.

Unanticipated Problems:

Affiliate Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the LCCC Multicenter Project Manager. The LCCC Multicenter Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:

Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the LCCC Multicenter Regulatory Associate prior to submission to their IRB.

9.8 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval

and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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11.0 Appendices

11.1 Appendix A. PROMIS SF v1.1 Global Health Questionnaire

	Please respond to each item by marking one box per row	**Excellent**	**Very good**	**Good**	**Fair**	**Poor**
Global 01	In general, would you say your health is:	5 □	4 □	3 □	2 □	1 □
Global 02	In general, would you say your quality of life is:	5 □	4 □	3 □	2 □	1 □
Global 03	In general, how would you rate your physical health?	5 □	4 □	3 □	2 □	1 □
Global 04	In general, how would you rate your mental health, including your mood and your ability to think?	5 □	4 □	3 □	2 □	1 □
Global 05	In general, how would you rate your satisfaction with your social activities and relationships?	5 □	4 □	3 □	2 □	1 □
Global 09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)	5 □	4 □	3 □	2 □	1 □
		Completely	**Mostly**	**Moderately**	**A Little**	**Not At All**
Global 06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	5 □	4 □	3 □	2 □	1 □
	In the past 7 days	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
Global 10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	5 □	4 □	3 □	2 □	1 □
		None	**Mild**	**Moderate**	**Severe**	**Very Severe**
Global 08	How would you rate your fatigue on average?	5 □	4 □	3 □	2 □	1 □
Global 07	How would you rate your pain on average?	□ □ □ □ □ □ □ □ □ □ □ 0 1 2 3 4 5 6 7 8 9 10 No pain Worst pain				

11.2 Appendix B. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

4. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
5. 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.
6. 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 participants for signs and symptoms of pneumonitis • Evaluate participants 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 participants 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). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not
	Grade 4	**Permanently discontinue**		

				feasible, fluid and electrolytes should be 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 participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants 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 discontinue1**		
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 discontinue1**		
Hypothyroidism	**Grade 2-4**	**Continue**	• Initiate thyroid replacement hormones (eg, levothyroxine	• Monitor for signs and symptoms of thyroid disorders.

			or liothyroinine) per standard of care	
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 and/or exclude other causes
	Grade 3	**Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis**		
	Grade 4 or recurrent Grade 3	**Permanently discontinue**		

2. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants 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).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

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 4.

Table 4 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 participant 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 (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant 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 (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
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		