CLINICAL STUDY PROTOCOL SLS17-201/ MK3475-770

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A PHASE 1/2 STUDY OF GALINPEPIMUT-S IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH SELECTED ADVANCED CANCERS

PROTOCOL NUMBER SLS17-201/MK3475-770

PROTOCOL v1.1

AMENDMENT 1.0

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Date of Original Protocol:	8 January 2018 (original protocol)
Date of Protocol v1.1 (Amendment 1.0):	12 April 2019

CONFIDENTIAL

The study will be conducted according to the International Council on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice (ICH GCP).

Protocol Approval – Sponsor Signatory

Study Title	A Phase 1/2 Study of Galinpepimut-S in Combination with Pembrolizumab (MK-3475) in Patients with Selected Advanced Cancers
Protocol Number	SLS17-201/MK3475-770
Protocol Date	08 January 2018 (original)
Date of Protocol v1.1 (Amendment 1.0)	12 April 2019

Protocol v1.1 (Amendment 1.0) accepted and approved by:

Chief Medical Officer and Study Medical Monitor
SELLAS Life Sciences Group, Inc.

Nicholas Sarlis, MD, PhD, FACP

Chief Medical Officer

SELLAS Life Sciences Group, Inc.

15 West 38th Street; 10th Floor
New York, NY 10018

United States of America

12 April 2019

Signature Date

Protocol Approval –Study Master Principal/Coordinating Investigators

Study Title	A Phase 1/2 Study of Galinpepimut-S in Combination with Pembrolizumab in Patients with Selected Advanced Cancers
Protocol Number	SLS17-201/ MK3475-770
Protocol Date	08 January 2018 (original)
Date of Protocol v1.1 (Amendment 1.0)	12 April 2019

Protocol accepted and approved by:

Co-Principal/Coordinating Investigators

United States

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<On file> 12 April 2019

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<On file>	12 April 2019
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Declaration of Investigator*

I have read and understood all sections of the protocol entitled "A Phase 1/2 Study of Galinpepimut-S in Combination with Pembrolizumab (MK-3475) in Patients with Selected Cancers", Protocol v1.1 (Amendment 1.0), and the accompanying investigator's brochures, version 2.0, dated 08 June 2017 for galinpepimut-S and edition 16, dated 29 June 2018 for pembrolizumab.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol v1.1, Amendment 1.0, dated 12 April 2019, the International Council on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice (ICH GCP) and all applicable government regulations. I will not make changes to the protocol before consulting with SELLAS Life Sciences Group or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. I will protect patient confidentiality and patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from SELLAS Life Sciences Group.

<Signature >	<DD/MM/YYYY>
Signature of Principal Investigator*	Date

<Name>

Printed Name of Principal Investigator*

*: Declaration Form for Individual Participating Clinical Site P.I.'s

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Protocol Synopsis

Protocol Number:	SLS17-201/MK3475-770
Title:	A Phase 1/2 Study of Galinpepimut-S in Combination with Pembrolizumab (MK-3475) in Patients with Selected Advanced Cancers
Protocol version	1.1
Study Amendment #	1.0
Sponsor:	SELLAS Life Sciences Group, Inc. 15 West 38th Street; 10th Floor New York, NY 10018 United States of America Telephone: +1-917-438-4352 FAX: +1-917-634-3413
Study Phase:	1/2
Study Sites:	Up to 20 centers in the United States.
Indication:	Colorectal (third or fourth line), ovarian (second or third line), small cell lung cancer (second line), breast cancer (triple negative; second line), acute myelogenous leukemia (unable to attain deeper response than partial on hypomethylators and who are not eligible for allogeneic hematopoietic stem cell transplant). For all the solid tumor indications, the highest citable number of lines of the therapy above is the maximum allowed for eligibility, i.e., patients who have received subsequent lines of therapy are ineligible.

Rationale:

There is clearly an unmet need for novel and effective therapy to improve responses and prolong disease remission/progression-free intervals already achieved with checkpoint blockade monotherapy (Farkona et al, 2016). The objectives of this proposed clinical study are: (i). to explore clinical outcomes (safety and potentially promising activity) in tumors using a combination of agents that improve immune-mediated anticancer effects, namely pembrolizumab and galinpepimut-S, and (ii). to maximize the chances of detecting a clinically meaningful efficacy signal in comparison to historical monotherapy data (with pembrolizumab alone) for further validation in larger, randomized trials.

To meet these objectives, the current design of a Phase 1/2 open-label, non-comparative, multicenter, multi-arm clinical study was chosen, as it has been used successfully in similar studies before (Menis et al, 2014; Toulmonde et al, 2018; Goldberg et al, 2016), and therefore considered as highly suitable for this trial.

The rationale behind this clinical study consist of 2 parts: a general strategy and a specific approach choosing Wilms Tumor-1 (WT1) protein as a direct immunization target and the selection of specific tumors for inclusion. Up to 5 tumor types will be included: colorectal cancer (CRC), ovarian cancer (OvC), small cell lung cancer (SCLC), triple-negative breast cancer (TNBC), and acute myeloid leukemia (AML).

Immune activation, suggested by the presence of infiltrating cytotoxic T cells in tumors, as well as eventual maintenance of a long-term proimmune status against the

tumor via memory T cells, have shown be associated with a better prognosis across a wide variety of malignancies (Reeves et al, 2017; Wölfl M et al, 2014). Therapies blocking programmed death receptor-1 (PD-1), such anti-PD-1 monoclonal antibodies, have shown the ability to reduce inhibitory immune signals within the tumor microenvironment (TME), thus allowing cytotoxic T cells to infiltrate the tumor and cause tumor regression in an expanding group of human malignancies, leading to a series of regulatory approvals and clinical usage on a global scale (Interkofer et al, 2013; Kyi et al, 2014; Spranger et al, 2016). These advances notwithstanding, there is significant room for improvement in the depth, frequency, and duration of antitumor responses with anti-PD1 agents. This provides a strong rationale for developing strategies to prime a host (cancer patient) with tumor-specific cytotoxic T cells targeted to specific tumor antigens via host administration while increasing the likelihood of significantly amplifying such a specific response with an anti-PD1 therapy (in this case, pembrolizumab), as well as prolong the duration of such a response (Perez-Gracia, et al, 2014) by both mitigation of tolerance and via induction of memory T cells [Marzo et al, 2000]). Thus, combining innovative, highly tolerable actively immunizing agents, such as peptide vaccines against well-validated high-antigenicity tumor targets, with anti-PD-1 products, such as pembrolizumab (Keytruda®) represents a highly attractive strategy, which deserves assessment in the clinical setting (Parchment et al, 2016; Drake CG, 2012).

The Wilms Tumor-1 (WT1) protein, the WT1 oncogene product, was first identified in childhood renal tumors, but has

been found to be overexpressed in a high proportion of solid and hematological malignancies, while its expression is substantially void in most healthy adult tissues (Wagner et al, 2014). Each WT1 protein isoform has different DNA binding and transcriptional activities, and can positively or negatively regulate various genes involved in cellular proliferation, differentiation, apoptosis, organ development, and sex determination (Haber et al, 1991). Although originally described as a tumor suppressor gene, the WT1 proteins appear to be involved in tumorigenesis as a bona fide oncogene (Keilhoz et al, 2005; Lindstedt, et al, 2014). As WT1 is a transcription factor and is not expressed intact in the cell membrane, it has not been able to be targeted (druggable) with either small molecules or monoclonal antibodies (Toska et al, 2014). Nonetheless, the protein is processed by the proteasome in tumors and the derived peptides are presented in a major histocompatibility complex (MHC)-dependent manner on the cell surface. Furthermore, WT1 peptide fragments when administered as direct immunogens (vaccines) are also taken up by antigen-presenting cells (APCs) and processed by the immunoproteasome for MHC-dependent presentation (Jiagirdar et al, 2016; Asemissen et al, 2006; Müller et al, 2003). Thus, WT1 is a highly attractive target for immunotherapy (Oka et al, 2002; Oka et al, 2007). WT1 was ranked as the top cancer antigen by a working group organized by the National Cancer Institute (NCI) in 2009 (Cheever, et al, 2009). The strong expression of WT1 protein in assorted cancers, coupled with its proposed mechanism of antigenicity and induction of immune responses (both CD4 and CD8 [Chapuis et al, 2013; Dao et al,

2016; Tyler et al, 2013; Tyler and Koehne, 2013; Fujiki et al, 2008; Krug et al; 2010]); after direct immunization against WT1 in patients with assorted cancers), makes it a rational candidate for the development of specific immunotherapies, such as peptide vaccines (Van Driesshe et al, 2012; Oka and Sugiyama, 2010; Oka et al, 2009; Dao and Seheinbert, 2008).

Galinpepimut-S is a directly immunizing therapy (a vaccine-like proprietary mixture of carefully selected heteroclitic and native WT1 peptide fragments) proven to produce WT1-specific T-lymphocytes in patients that could target a patient's cancer (Gomez-Nunez et al, 2006; Pinilla-Ibarz et al, 2006; Bleakley and Ridell, 2011; May et al, 2007; Brayer and Pinilla-Ibarz, 2013). Additionally, galinpepimut-S monotherapy has previously shown promising clinical activity in both pilot and Phase 2 studies in patients with AML, malignant pleural mesothelioma (MPM), high-risk multiple myeloma, and ovarian cancer (OvC) in a minimal residual disease (MRD) setting (Maslak et al, 2010; Krug et al 2010; Brayer et al, 2015; Maslak et al, 2016; Maslak et al, 2018; Zauderer et al, 2016; Zauderer et al, (iMig), 2016; Zauderer et al, 2017; Koehne et al 2017; http://e-materials.com/ebmt2017/#/presentation/16745; https://learningcenter.ehaweb.org/eha/2017/22nd/181028/guenther.koehne.wt1.heteroclitic.epitope.immunization.following.autologous.html; Koehne et al, 2018; O'Cearbhaill et al, 2018; Tsuboi et al, 2012). Galinpepimut-S is generally well tolerated. (SELLAS, Data on file; Brayer et al, 2015; Zauderer et al, 2017; Maslak PG et al, 2018; Koehne et al, 2017; O'Cearbhaill et al, 2018; Galinpepimut-S Investigator Brochure v2.0, 08 June 2017).

Therefore, combining galinpepimut-S with the checkpoint inhibitor pembrolizumab, which beneficially and profoundly alters the TME (among other potent immunostimulatory effects in the host), is hypothesized to increase the proportion of patients who develop an immune response against their cancer and potentially improve their clinical outcome over pembrolizumab monotherapy, without the burden of additional toxicities in macroscopically measurable malignancies.

In this clinical trial, for each chosen tumor type to be studied, we will investigate whether galinpepimut-S administered concomitantly with granulocyte-macrophage colony-stimulating factor (GM-CSF) and the well-characterized adjuvant Montanide (van Doorn et al, 2016; Montanide IB 2015; Aucouturier et al, 2002; Aucouturier et al, 2001; Tovey and Lallemand, 2010) can be safely administered with pembrolizumab. We postulate that galinpepimut-S will induce a WT1-specific immune response, which will be associated with enhancement of the efficacy of anti-PD1 monotherapy when considered in the context of historical controls, as assessed by overall response rate (ORR), as well as duration of response (DOR), and well as exploratory endpoints including WT1-specific immune response dynamics and overall survival (OS), will be investigated. If this pilot study meets the primary efficacy endpoint of ORR for a given tumor type, a randomized Phase 2 trial would be warranted in that tumor type.

The tumor types selected for this trial (CRC, OvC, SCLC, TNBC, and AML) have been documented to commonly express WT1, and this trial will select patients whose tumors are positive

for WT1 expression. The choice of these tumor types was based on specific features of each malignancy.

Colorectal cancer (CRC): WT1 expression has been documented to be expressed in between 70 to 90% of patients with CRC (Miyata et al, 2007; Oji et al, 2003; Bejrananda et al, 2011). Patients with microsatellite-stable (MSS) tumor genetics make up between 80 to 90% of cases (Naboush et al, 2017; Diaz and Le, 2015). Patients will have microsatellite (MS) instability (MSI) status tested in their primary tumors and will be classified as MSI-high (H) and -low (L) (Pawlik et al, 2004; Morán et al, 2010; Supek and Lerner, 2015; Goldstein et al, 2014). The focus will be on MSI-low tumors, but no entry selection will be applied based on this tumor feature. In several clinical trials in MSI-L CRC, anti-PD-1 agents have shown to induce 0 to 5% ORR (Link and Overman, 2016; http://www.targetedonc.com/publications/targeted-therapies-cancer/2017/2017-february/immune-checkpoint-inhibitors-in-crc; Boland and Ma, 2017; Myint and Goel, 2017; Overman et al, 2016; Segal et al, 2016; Bendell et al, 2016; Overman et al, 2016; Andre et al, 2017). This is in contrast to the significant activity of PD1 blockade in MSI-H CRC, the basis for the recent Food and Drug Administration (FDA) approval of pembrolizumab in MSI-H cancers (including CRC) (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm). Only those CRC patients with MSI-L and MSS will be included in the efficacy analyses.

Ovarian cancer (OvC): WT1 expression is highly prevalent in OvC (Dupont et al, 2004). The degree of expression is high enough that pathologists routinely use IHC stains for WT1 with

a standardized convention for describing its expression to help distinguish epithelial ovarian cancers from other ovarian/fallopian tumors (Al-Hussaini et al, 2004). WT1 is a particularly sensitive and specific marker for serous ovarian cancer (Acs, et al, 2004).

Small-cell lung cancer (SCLC): WT1 expression has not been studied in SCLC as extensively as in non-SCLC (NSCLC), mainly due to the relative rarity of the former. Nonetheless, WT1 positivity is higher (40 to 83%) in SCLC versus NSCLC (Babiak et al, 2014; Menssen et al, 2000; Oji et al, 2002; Wang et al, 2013). The activity of anti-PD1 agents in SCLC in the second line of therapy is reflected in ORR values of about 33 to 37% (Ott et al, 2016; Hellman et al, 2016; Antonia et al, 2016; Riess et al, 2016).

Triple-negative breast cancer (TNBC): Although WT1 expression occurs in 70 to 80% of patients with basal-type breast cancer, in specimens from TNBC (Provenzano et al, 2016; Domfeh et al, 2008), WT1 expression is approximately 8 to 15%. Nonetheless, this value may represent low sensitivity of currently used, commercially available anti-WT1 monoclonal antibodies used for IHC (Ichinohasama 2010). Additionally, WT1 has been found to be focally amplified in a significant proportion of TNBCs and hence is still a valid immuno-oncology target, despite its low abundance observed (Craig et al, 2012).

Acute myeloid leukemia (AML): WT1 is strongly and prevalently (90 to 95% of cases) expressed in AML blasts both in the peripheral blood (PB) and bone marrow (BM) (Inoue et al, 1998; Hosen et al, 2002; Keilholz et al, 2005; Cilloni et al

2009; Menssen et al, 1995; Inoue et al, 1997). It is also expressed in leukemic stem cells (LSCs) (Saito et al 1997; Yong et al, 2008). WT1 expression is reliable enough to be used as a marker of MRD in AML (as a molecular marker of relapse/response) (Alonso-Dominguez et al, 2012; Messina et al, 2014; Ogawa et al, 2003; Candoni et al, 2009; Hämäläinen et al, 2008; Mulé et al, 2016) and is typically included in MRD diagnostic multi-gene panels (Buccisano et al, 2017). To date, anti-PD1 therapies have shown modest activity in relapsed AML (second line) in combination with hypomethylating agents (Lichtenegger et al, 2017; Haroun et al, 2017) as reflected in ORR values of up to 34% in that setting (Daver et al, 2016; Daver et al, 2017; Nagler et al, 2017; Krupka et al, 2016; Sehgal et al, 2015; http://www.targetedonc.com/publications/targeted-therapies-cancer/2017/2017-february/immune-checkpoint-approaches-in-aml-and-mds-a-next-frontier; Chien et al, 2018; Daver et al, 2018).

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers
- To evaluate the anti-tumor activity of the combination of galinpepimut-S and pembrolizumab as defined by Response Criteria in Solid Tumors (RECIST) 1.1 and Immune-related Response Criteria in Solid Tumors (iRECIST) to determine if the activity seen, as measured by ORR, is sufficiently promising to evaluate the combination in future clinical studies. For AML patients: to study the possibility of achieving morphologic

complete response (CR; including CR with incomplete recovery of blood counts or platelets [CRi/CRp]).

Hypothesis for the Primary Objectives: Combining galinpepimut-S with pembrolizumab could increase the clinical benefit of pembrolizumab monotherapy (Seledstov et al, 2015; Kleponis et al, 2015) as assessed by improved ORR values versus historical controls for each individual tumor type tested. This would constitute a "positive efficacy signal" (as relevant to each particular tumor type tested) and warrant broader future clinical investigations. Further, the combination will not increase the burden of toxicities and will have an overall similar/comparable adverse event (AE) profile as pembrolizumab monotherapy.

(N.B.: The a priori statistical assumptions and threshold criteria supporting the definition of a positive signal are described in detail in Section 7.6.).

Secondary Objectives:

- To evaluate the clinical benefit of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers through the analysis of time to response (TTR), time to next treatment, and duration of response (DOR)

Hypothesis for the Secondary Objectives: Galinpepimut-S in combination with pembrolizumab could increase the clinical benefit of pembrolizumab monotherapy upon parameters other than ORR, such as TTR, time to next treatment, and DOR. In

case of a positive efficacy signal, such effects could be correlated with effects on ORR (vs. historical controls).

Exploratory Objectives:

- To further characterize the immunogenicity profile of galinpepimut-S when administered in this combination, i.e., its ability to generate WT1-specific immunocyte responses through analyses of WT1-specific CD8 and CD4 cells in PB, as well as WT1-specific memory CD8 T cells, myeloid-derived suppressor cells [MDSC], and T-regulatory cells (Treg) in PB
- To gauge the general immunodynamics effects upon non-antigen-specific lymphocyte immunophenotypic subtypes will be studied in PB via flow cytometry
- To assess the effects of the combination on defined biomarkers of immune checkpoint activity in the tumors (or bone marrow for AML patients) and their surrounding microenvironment (pharmacodynamics specific to pembrolizumab)
- To assess the association between selected biomarker readouts and clinical efficacy measures at specific time-points, using pre-treatment and on-treatment tumor biopsies
- To assess OS and progression-free survival (PFS)
- To assess the rate of achievement of MRD negativity (for patients in the AML arm only).

Hypothesis for Exploratory Objectives: Combining galinpepimut-S with pembrolizumab could lead to the development of a robust WT1-specific immune response

against patients' cancers, and potentially improve the abundance and functionality of the hosts' immunocytes within the TME (versus pembrolizumab monotherapy) (Duraiswamy et al, 2013). Positive correlative analyses (as relevant to a particular tumor type) between immune and clinical outcomes would provide a mechanism of action (MOA) framework to inform the design of future larger, randomized clinical studies in that tumor type.

Overall Study Design: This is a Phase 1/2, open-label, non-comparative, multicenter, multi-arm study of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers. This study will assess efficacy and safety of galinpepimut-S and pembrolizumab on various tumor types. Patients will be followed long-term for OS and safety.

The general principles regarding the schedule of administration of the investigational therapies will be as follows:

Overall Treatment Investigational Administration Schedule

The first 2 galinpepimut-S injections will initially be administered as monotherapy every 3 weeks (Week 0 and Week 3). Thereafter, galinpepimut-S will be co-administered with pembrolizumab every 3 weeks for 4 additional administrations (for the galinpepimut-S initial immunization induction phase series; weeks 6-15) to coincide with the per label pembrolizumab dosing frequency. After that, there will be one un-paired administration of pembrolizumab (week 18), and then galinpepimut-S will be resumed on an every 3-week schedule for 6 additional doses (early immune booster phase; weeks 21-36). At the end of this phase, there will be a 12-week interval where 3 unpaired administrations of pembrolizumab

will occur (weeks 39-45), and then galinpepimut-S will be resumed on an every 12-week schedule for 4 additional doses (late immune booster phase; weeks 48-84). After 84 weeks, continuing non-progressed patients will be treated with pembrolizumab alone up until week 111.

Galinpepimut-S will be administered 30-60 minutes after the completion of IV infusion of pembrolizumab on Day 1 of each cycle during which the 2 drugs are being co-administered.

Pembrolizumab will be administered at a dose of 200 mg intravenously every 3 weeks on Day 1 of each cycle (3-week cycles) starting on Study Week 6 and continuing for up to 2 years thereafter (Study Week 111).

To monitor for any adverse reactions, specifically for systemic anaphylaxis type reactions against either GM-CSF or galinpepimut-S, patients will remain in the clinic for approximately 30 minutes following each GM-CSF or galinpepimut-S injection.

Safety assessments will be conducted at every visit. The end of treatment (EOT) visit will occur 30 days after the last injection.

Specifically for patients in the AML arm, the timing of the administration of the investigational therapies (pembrolizumab and galinpepimut-S) with respect to administration of hypomethylating agents (HMAs) will be as follows:

- AML patients on cycles #1 – 4 of HMA on-label therapy (treated according to standard clinical care) will be pre-screened to gauge potentially eligibility for the study.
- If restaging bone marrow biopsy immediately after the completion of cycle #4 of HMA therapy demonstrates

	morphological partial response (PR), then such patients become eligible for the study and can initiate investigational therapy (pembrolizumab and galinpepimut-S), as long as the latter commences prior to the initiation of cycle #5 of the HMA. • Reasonable efforts will be made by the Contracted Research Organization (CRO), Cancer Insight, LLC, at actively enrolling clinical sites to initiate investigational therapy within 14 +/7 days from the completion of cycle #4 of HMA therapy, to ensure relative homogeneity in the initiation timing relationship between the two therapeutic modalities, i.e., HMA and investigational therapy. Furthermore, for clarification purposes, each cycle of therapy in patients in the AML arm will be defined by the frequency of administration of the study investigational agents (pembrolizumab and galinpepimut- S), i.e., 3 weeks. This clarification is important, because: a. patients in the AML arm will continue their HMA therapy throughout the administration of study investigational agents and b. the timing of initiation between HMA cycle #5 and that of the first administration of investigational therapies are de-linked.
Number of Patients	Approximately up to 90 patients will be enrolled in the study. The planned number of patients within each tumor-specific cohort is as follows: CRC (N = 20), OvC (N = 20), SCLC (N = 20), TNBC (N = 15), and AML (N = 15).

Summary of Subject Key Eligibility Criteria:

For inclusion in the study, patients will be:

- Male or female ≥ 18 years of age at the time of signing the informed consent form, have histologically or cytologically-confirmed advanced or metastatic solid tumors (CRC, OvC, SCLC, or TNBC) or AML with best response of "partial response" (PR) after 4 cycles of HMA therapy (per European LeukemiaNet [ELN] criteria). All tumor types will also meet their additional cohort-specific requirements (see Section 4.1. below).
- Specifically for patients in the AML arm, the following subject subgroups are eligible:
  - Frontline (1st line) patients treated with HMAs since their initial AML diagnosis
  - Patients who have required cytoreductive therapy with hydroxyurea or leukapheresis at the time of their initial AML diagnosis, and who subsequently seamlessly transitioned to HMA therapy
  - Subjects who have experienced induction early failure after initial therapy with 1 - 2 cycles of a standard chemotherapy ("7+3" and similar regimens) and subsequently immediately treated with HMAs

  as long as such patients have achieved PR as their best observable response after 4 cycles of HMA therapy (per European LeukemiaNet [ELN] criteria).
- At the time of screening for study entry, patients' tumor material (or bone marrow [BM] for AML) will be tested for WT1 expression via immunohistochemistry (IHC) as follows: in the solid tumor arms, in both their initial

primary tumor and recent biopsy of metastatic disease, whereas in the AML arm in leukemic blasts (either in the BM or PB) at the time of initial diagnosis. .

- At the time of screening for study entry, patients in the solid tumor arms should have measurable disease based on RECIST 1.1 criteria, whereas in the AML arm should have evidence of morphologic partial response (decrease of BM blast percentage to 5% to 25% and decrease of pretreatment BM blast percentage by > 50%) but absence of extramedullary disease, as defined initially by the AML Working Group Criteria (Cheson et al, 2003) and also quoted in the more recent ELN criteria (Döhner et al, 2010). In both arms, tumor/leukemic blast burden will be determined by a local site investigator (physician) upon clinical and imaging/BM morphologic assessment..
- Adequate organ function as defined in Table 1 and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

For a full list of eligibility criteria, refer to Sections .

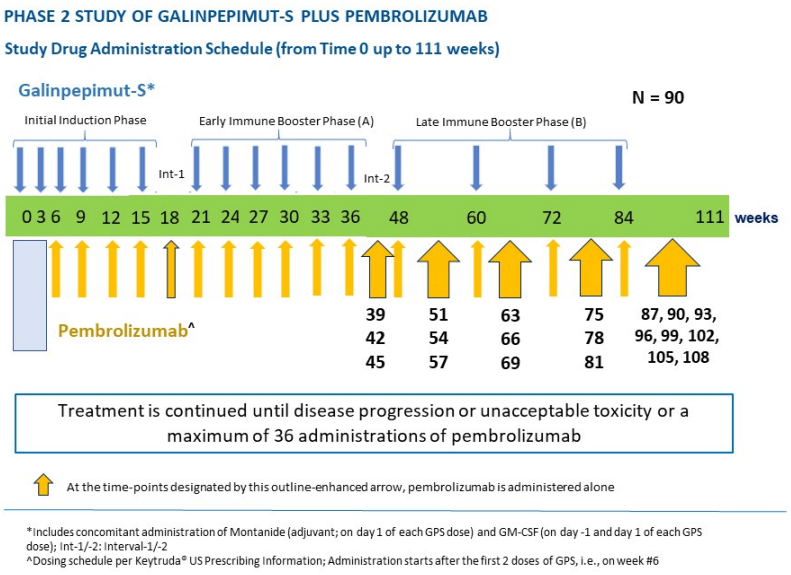
Treatments:

Patients will be administered a fixed dose of the following treatments:

- Galinpepimut-S: 4 WT1 derived synthetic analog peptides (galinpepimut-S) emulsified with the adjuvant Montanide for a total injection volume of 1 mL.
- Pembrolizumab: 200 mg

Patients will be administered subcutaneous (SC) sargramostim (from here on referred to as GM-CSF) at the site of the planned galinpepimut-S injection 2 days before (Day –2) and the day of (Day 1) each galinpepimut-S administration.

The overall treatment administration schedule is shown in the figure below:



Refer to Section 5 for more details on treatment.

Dose-limiting Toxicities

All toxicities will be graded using NCI CTCAE Version 5.0 (published in November 2017), as per the following link:. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Q uick_Reference_5x7.pdf.

The dose-limiting toxicity (DLT) window of observation will be:

For patients in the solid tumor arms: at least one (1) cycle following the co-administration of galinpepimut-S in combination with pembrolizumab.

For patients in the AML arm: at least 8 weeks following the first administration of pembrolizumab

N.B.: this DLT assessment time window at the beginning of the study was chosen considering that (i). the treatment regimen in AML subjects includes the administration of HMA treatment (with cycle duration of at least 4 weeks), along with investigational therapy (pembrolizumab and galinpepimut-S), and (ii). the timing of administration of the two sets of modalities is not linked, so that an adequate time interval to capture potential toxicities is secured.

A DLT is judged by the investigator to be possibly, probably, or definitely related to study drug administration.

For patients in the solid tumor arms:

Missing > 25% of the doses as a result of drug-related AE(s) during the period from first administration of galinpepimut-S

and up until the completion of the first cycle of the co-administration of galinpepimut-S in combination with pembrolizumab, drug-related AE(s) which caused patient to discontinue treatment during Cycle 1, or Grade 5 toxicity, will be considered DLTs.

DLTs will also be defined as most Grade 4 nonhematologic toxicities (not laboratory) or hematologic toxicity lasting ≥ 7 days except thrombocytopenia, most nonhematologic AEs ≥ Grade 3 in severity, febrile neutropenia (FN) Grade 3 or Grade 4: missing >25% of pembrolizumab doses as a result of drug-related AE(s) during the first cycle, thrombocytopenia < 25,000/mm^3 and meeting specific criteria, including a life-threatening bleeding event, or prolonged delay (> 2 weeks) in initiating the second cycle of of co- administration of galinpepimut-S in combination with pembrolizumab due to treatment-related toxicity. Details for DLTs are provided in Section 5.3.6.1.

Staggered Early Enrollment:

To minimize exposing subjects to the risk of potential unknown acute and subacute toxicities of combining pembrolizumab with galinpepimut-S, the inter-dosing interval in-between the first consecutive three (3) subjects to be enrolled in this study arm will be one (1) week following the administration of the first dose of pembrolizumab in these patients.

DLT assessment and actions (unless stopping rules apply):

Initially up to 6 patients will be enrolled across all active solid tumor cohorts (colorectal, ovarian, small cell lung cancer, breast cancer). If 2 or fewer patients of these first 6 patients have DLTs, enrollment can continue for up to another 6 patients

across these arms with no dose adjustments made. If DLTs are observed in more than 2 patients of the first 6, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the immediately subsequent administration after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable. In the next 6 patients (patients 7 to 12), if again, 2 or fewer of these patients have DLTs observed, enrollment can continue. If DLTs are observed in more than 2 of patients 7 to 12, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled, while keeping the pembrolizumab dose and frequency stable. If DLTs are observed in more than 2 patients of the first 6 (patients 1 to 6) and again in more than 2 patients of the next 6 (patients 7 to 12), the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the 2 immediately subsequent administrations after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.

Should a given patient experience any of the above DLTs at any time after the completion of the first cycle of co-administration of galinpepimut-S in combination with pembrolizumab, the frequency of administration of galinpepimut-S will be reduced by 50% for the next cycle, but pembrolizumab will continue as

scheduled. If another DLT occurs in that next cycle, the frequency of administration of galinpepimut-S will be reduced by 50% for the subsequent 2 cycles, but pembrolizumab will continue as scheduled. If a DLT occurs after these dose modifications in subsequent cycles, the patient will be discontinued from the study.

The above dose density modifications in response to DLTs is further summarized in the bulleted list of actions below:

- First DLT → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **once thereafter**, i.e. **for 1 additional cycle** → DLT resolution → Return to per protocol schedule of GPS administration
- Second DLT (after reverting to the per protocol schedule) → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **twice thereafter**, i.e. **for 2 additional cycles** → DLT resolution → Return to per protocol schedule of GPS administration
- Third DLT (occurring either after reverting to the per protocol schedule or during the 'spread out' schedule to manage the 2nd DLT above) → Discontinue patient from study.

N.B.: In all above modifications of the dose density of galinpepimut-S, as all intervals (in weeks) between 2 successive GPS administrations are multiples of three (3) by design, following these rules, co-administration with pembrolizumab is always secured.

Stopping Rules:

- Development of any SAEs at least "possibly attributable" to the study agent(s) in 2 out of the first 6 patients in the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.
- The fraction of patients experiencing an SAE at least "possibly attributable" to the study agent(s) exceeds 1/3, at any time during study implementation beyond the first 6 patients.
- Death at least "possibly attributable" to the study agent(s) within 30 days after the administration of the investigational treatment (GPS plus pembrolizumab).

If the study is stopped due to activation of the above rules, the safety data will be examined by the sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study at large.

For patients in the AML arm:DLTs will be defined by toxicities observed in the first 8 weeks from study entry, as follows:

a. Missing > 25% of the doses as a result of drug related AE during cycle 1 and/or 2

b. Drug-related AE which causes patient to discontinue treatment during cycle 1 and/or 2

- Grade 5 toxicity

- Grade 4 non-hematological toxicity (other than laboratory abnormality)

- Grade 3 non-hematological toxicity (other than laboratory abnormality; exception: fatigue, nausea, emesis, diarrhea, rash, infection, fever, or bleeding unless the event lasts more than 3 days despite optimal care)

- Grade 3 and 4 non-hematological lab abnormality, if any of the following occurs:

- Medical intervention is required
- Abnormality persists > 1 week
- Abnormality results in drug-induced liver injury
- Any treatment-related toxicity that causes a greater than 3-week delay in initiation of cycle 2 and/or 3
- Development of an immune-related AE resulting in withholding of pembrolizumab and initiation of steroids, for example, grade 2 or higher colitis/diarrhea, grade 2 or higher pneumonitis, grade 2 or higher transaminitis, any grade myocarditis (complete list currently shown in Table 5)

Any other toxicities in the AML arm will not be considered dose-limiting. Details for AML DLTs are provided in Section 5.3.6.2.

Staggered Early Enrollment:

To minimize exposing subjects to the risk of potential unknown acute and subacute toxicities of combining HMA with the investigational therapy (pembrolizumab and galinpepimut-S) in the AML arm, the inter-dosing interval between the first two (2) subjects to be enrolled in this study arm will be 12 weeks.

DLT assessment and actions (unless stopping rules apply):

AML-specific DLTs will be considered separately from all other patients. Initially up to 6 patients will be enrolled in the AML cohort. If 2 or fewer patients of these first 6 patients have DLTs, enrollment can continue for up to another 6 patients in the AML arm with no dose adjustments made. If DLTs are observed in more than 2 patients of the first 6, the time interval between galinpepimut-S doses will be doubled for the inoculation following the one associated with the DLT, but pembrolizumab will continue as scheduled.

In the next 6 patients (patients 7 to 12), if again, 2 or fewer of these patients have DLTs observed, enrollment can continue. If DLTs are observed in more than 2 of patients 7 to 12, If DLTs are observed in more than 2 of patients 7 to 12, the time interval between galinpepimut-S doses will be doubled for the inoculation following the one associated with the DLT, but pembrolizumab will continue as scheduled.

If DLTs are observed in more than 2 patients of the first 6 (patients 1 to 6) and again in more than 2 patients of the next 6 (patients 7 to 12), the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT, but pembrolizumab will continue as scheduled. For example, if galinpepimut-S was given on a Q3W

schedule before the DLT occurred, it should be given Q6W for the 2 immediately subsequent administrations after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.

Should a given patient experience any of the above DLTs at any time after the completion of the second cycle of co-administration of galinpepimut-S in combination with pembrolizumab, the frequency of administration of galinpepimut-S will be reduced by 50% for the next cycle, but pembrolizumab will continue as scheduled. If another DLT occurs in that next cycle, the frequency of administration of galinpepimut-S will be reduced by 50% for the subsequent 2 cycles, but pembrolizumab will continue as scheduled. If a DLT occurs after these dose modifications in subsequent cycles, the patient will be discontinued from the study.

The above dose density modifications in response to DLTs is further summarized in the bulleted list of actions below:

- First DLT → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **once thereafter**, i.e. **for 1 additional cycle** → DLT resolution → Return to per protocol schedule of GPS administration
- Second DLT (after reverting to the per protocol schedule) → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **twice thereafter**, i.e. **for**

2 additional cycles → DLT resolution → Return to per protocol schedule of GPS administration

- Third DLT (occurring either after reverting to the per protocol schedule or during the 'spread out' schedule to manage the 2nd DLT above) → Discontinue patient from study.

N.B.: In all above modifications of the dose density of galinpepimut-S, as all intervals (in weeks) between 2 successive GPS administrations are multiples of three (3) by design, following these rules, co-administration with pembrolizumab is always secured.

Stopping rules:

- Development of any SAEs at least "possibly attributable" to the study agent(s) in 2 out of the first 6 patients in the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.
- The fraction of patients experiencing an SAE at least "possibly attributable" to the study agent(s) exceeds 1/3, at any time during study implementation beyond the first 6 patients.
- Death at least "possibly attributable" to the study investigational agent(s) within 30 days after the administration of the investigational treatment (GPS plus pembrolizumab)
- Development of grade 3 or higher colitis/diarrhea,

grade 3 or higher pneumonitis, grade 3 or higher nephritis, grade 3 or higher transaminitis, or any grade myocarditis in 2 out of the first 6 patients in the AML arm of the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.

- The fraction of patients experiencing grade 3 or higher colitis/diarrhea, grade 3 or higher pneumonitis, grade 3 or higher nephritis, grade 3 or higher transaminitis, or any grade myocarditis exceeds 40%, at any time during study implementation beyond the first 6 patients in the AML arm.

If the study is stopped due to activation of the above rules, the safety data will be examined by the Sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study at large.

Note: Dose modifications for HMA-related (known/expected) toxicities -for either azacitidine or decitabine- in AML patients will be based on the respective US Prescribing Information for these products. These documents are included as Appendices 12.1 and 12.2.

Procedures

After signing the informed consent, patients will enter the 28-day Screening period. At the baseline visit (Day −2), all pretreatment screening procedures/assessments must be completed, review of inclusion/exclusion criteria (including specific tumor histologic type verification, [e.g., TNBC]), and review of laboratory and tissue pathology results confirmed prior to enrollment and the first GM-CSF injection.

Patients will then enter the open-label treatment period which is approximately 111 weeks (777 days; 2.13 years) in duration; the last galinpepimut-S administration would occur at 84 weeks (day 588 days; 1.61 years).

Patients will be treated until progression, death, unacceptable toxicity (including activation of the stopping rules in either the solid tumor arms or the AML arm), or completion of 2 years of therapy with pembrolizumab, whichever occurs first.

A safety follow-up period will occur 30 days after the last administration of study drug. A follow-up phone call for serious adverse events will occur 90 days after the last dose of pembrolizumab or 30 days following cessation of study treatment if the patient begins new anticancer therapy, whichever is earlier. If the patient initiates new anticancer therapy, this must be reported by the investigator.

For a full list of study procedures, including the timing of each procedure, please refer to Section and the Schedule of Assessments in Table 8.

Estimated Study Duration:	Maximum study treatment duration is approximately 111 weeks (777 days; 2.13 years), during which the last galinpepimut-S administration would occur at 84 weeks (day 588 days; 1.61 years) – all time measurements assume t-zero the date of first galinpepimut-S administration, except specifically for safety, t-zero assumes the date of first GM-CSF administration (day -2 of the entire protocol schedule).
Efficacy Assessments:	Signal response for each a priori statistically defined clinical outcome (ORR per RECIST 1.1) for all solid tumor types or other appropriate instrument scales, such as attainment of morphologic CR in AML patients. In addition to RECIST 1.1, all scans will be read according to iRECIST immune response consensus guideline (Seymour et al, 2017) to ensure that patients are not discontinued from therapy due to the phenomenon of tumor "pseudoprogression", and clinical decisions will be based on iRECIST (Hodi et al, 2016).
Exploratory Assessments:	ORR per iRECIST in patients in the solid tumor arms and the frequency (rate) of achievement of MRD negativity in patients in the AML arm will be evaluated as exploratory endpoints. All patients enrolled in the study will be followed and assessed for PFS and OS, according to the intent-to-treat (ITT) principle. Specifically for OS, patients who complete the protocol-specified study treatment period or patients who discontinue early will enter an off treatment follow-up period to assess OS, with regular assessments every 3 months until study closure (defined as up to 2 years and 6 weeks, i.e., 111 weeks after the first galinpepimut-S administration given to the last patient

	enrolled into the study, which corresponds to 2 years after the first injection of pembrolizumab). This study will also assess the effect of the study treatment on readouts of immunologic tests in PB samples, as well as presence and density of immune cell infiltrates within the tumor stroma (or BM in AML patients) using at least one post-therapy tumor biopsy (and comparing the findings with those at baseline, i.e., prior to initiation of treatment). Details are provided in Section 6.3.
Safety Assessments:	At each galinpepimut-S administration visit the investigator will review concomitant medications, AEs, ECOG performance status score, vital signs (including body temperature, systolic and diastolic blood pressure [BP], heart rate, and respiratory rate; and weight). All blood samples will be collected before galinpepimut-S and/or pembrolizumab administration (Day 1 of each cycle). Blood samples for complete blood count (CBC) with differential and platelet count and serum chemistry, will also be collected prior to the administration of GM-CSF at Day -2 of each cycle whereby galinpepimut-S is also co-administered. In addition to the blood samples collected for safety, blood samples will be collected for exploratory investigations on immune reactivity against the tumor. Safety assessments will be conducted at every visit. The EOT visit will occur 30 days after the last pembrolizumab injection. A follow-up phone call for serious adverse events (SAEs) will occur 90 days after the last dose of pembrolizumab or 30 days following cessation of study treatment if the patient begins new anticancer therapy, whichever is earlier.

	Toxicity will be graded in accordance with CTCAE v5.0 developed by the NCI (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Details regarding mitigation steps if AEs occur during drug administration (e.g., injection site reactions [ISRs]) post-galinpepimut-S SC administration (when administered as monotherapy during the first 2 administrations, as well as subsequently, i.e., in combination with pembrolizumab IV infusion), as well as infusion related reactions (IRR) to pembrolizumab IV (when given in combination with galinpepimut-S SC) are included in Section 5.3.6.
Statistical Considerations:	**Sample Size:** Approximately 90 patients will be enrolled in the study. The planned number of patients within each tumor-specific cohort is as follows: CRC (N = 20), OvC (N = 20), SCLC (N = 20), TNBC (N = 15), and AML (N = 15). This study uses a Bayesian monitoring approach to guide decision-making using data on the primary efficacy endpoint (ORR for patients in the solid tumor arms and rate of achievement of CR/CRi/CRp in patients in the AML arm) within each tumor-specific cohort. If the data provide high confidence that the true ORR (or CR/CRi/CRp rate for AML) exceeds a minimal clinically meaningful level or threshold, then the results would support continued development (a "Go" decision) for that cohort. If the data suggest that the true ORR (or CR/CRi/CRp rate for AML) is unlikely to meet the desired level of clinical activity, then the results would support a decision to halt further continuation of accrual (a "Stop" decision) for that cohort. This approach is

based on the decision-making framework of Lalonde et al, 2007 and Frewer et al, 2016.

For each tumor type test, the minimal clinically meaningful level of any given ORR (or CR/CRi/CRp rate for AML) value/result is defined by the "lower reference value" (LRV), and the desired level of clinical activity is defined by the "target value" (TV). The LRV and TV for each tumor type are determined by a synthesis of medical opinion, evidence from the literature, or data from other compounds being developed in the same area. These values are as follows: CRC LRV=10%, TV=20%; OvC LRV=10%, TV=20%; SCLC LRV=30%, TV=40%; TNBC LRV=15%, TV=25%; AML LRV=15%, TV=25%.

Enrollment in a cohort may be stopped for futility prior to reaching the planned sample size if there is a high predicted probability of a Stop decision at the planned sample size. Enrollment in a cohort may be increased with approximately 10 additional patients beyond the planned sample size if the sponsor determines that further data is needed to clarify the safety or efficacy signals for a Go/No-Go decision.

Based on the performance characteristics computed and described in the statistical section of the protocol, the sample sizes are adequate to address the study's objectives. No formal statistical power calculations to determine sample size were performed.

Statistical Methods:

Analysis Sets

- The full analysis set (FAS) comprises all patients who are assigned to receive study treatment as per the intent-to-treat (ITT) principle, regardless of whether or

not they subsequently go on to receive study treatment or whether they deviate from the protocol in any major way.

- The modified intent-to-treat (mITT) set comprises all patients who are assigned to receive study treatment and have at least 1 post-baseline efficacy assessment (RECIST 1.1), even if they deviate from the protocol in any major way. The mITT will also include any patient that goes off study treatment because of clinical progression prior to the first scheduled per-protocol scan.
- The safety analysis set comprises all patients who receive any amount of study drug.
- The per-protocol set (PPS) comprises all patients who are assigned to receive study treatment, receive at least 1 injection of study treatment, have at least 1 post-baseline efficacy assessment (RECIST 1.1), and do not deviate from the protocol in any major way

All efficacy analyses will be based on the FAS and will also be conducted on the mITT set and PPS for exploratory purposes. The study's primary objective will be judged on the basis of the analysis of ORR. For CRC patients, only those with MSS and MSI-L will be included in the primary efficacy analysis. The safety analyses will be based on the safety analysis set and will group patients according to treatment actually received. Secondary and exploratory efficacy analyses will be performed on the FAS as well as on the mITT set and PPS for exploratory purposes.

Analysis of Primary Efficacy Endpoint: For each tumor-specific cohort, a Bayesian approach with non-informative

Jeffreys prior beta distribution with parameters a = 0.5 and b = 0.5 will be used to estimate the ORR (or CR/CRi/CRp rate in AML) and its 95% credible interval based on the posterior distribution.

At the time of analysis, within each tumor-specific cohort, the prior distribution will be updated with all available data from the evaluable patients to obtain the posterior distribution of the true ORR. The posterior probabilities that ORR (or CR/CRi/CRp rate in AML) exceeds TV and LRV will be reported for each cohort. A high posterior probability that ORR > LRV will support a "Go" decision to continue development in the cohort, and a low posterior probability that ORR > TV will support a "Stop" decision to halt development in the cohort. A "Consider" decision results if neither a Stop nor a Go decision can be made. The specific criteria for making a Stop, Consider, or Go decision within each tumor-specific cohort are derived using the following acceptable risks:

- 10% false stop risk: maximum acceptable probability that ORR > TV given that a Stop decision is made.
- 20% false go risk: maximum acceptable probability that ORR ≤ LRV given that a Go decision is made

Before reaching the planned sample size in a cohort, the posterior probabilities will be updated continuously after each patient (or group of patients) and will be used to determine, within each cohort, the predictive probability of eventually reaching a Stop decision at the planned sample size. If this predictive probability is ≥ 80%, then enrollment in that cohort may be stopped early for futility.

Stop/Go and futility decision criteria are non-binding and may be regarded as guidance and information to be integrated with a full medical review of safety and efficacy data observed at the time of analysis in determining the next course of action. No tests of statistical significance are planned.

CRC

Given a sample size of 20 patients in the CRC (third/fourth line) group, where TV = 20% and LRV = 10%, the decision criteria are as follows: Go if ≥ 4 responses observed (20%); Stop if ≤ 1 responses observed (5%). With these criteria, there is a 59% probability of a Go decision and 7% probability of a Stop decision if the true ORR is 20%, and there is a 13% probability of a Go decision and 39% probability of a Stop decision if the true ORR is 10%.

OvC

The same sample size, TV, LRV, decision criteria, and probability statements as the CRC group apply.

SCLC

Given a sample size of 20 patients in SCLC group, where TV = 40% and LRV = 30%, the decision criteria are as follows: Go if ≥ 8 responses observed (40%); Stop if ≤ 5 responses observed (20%). With these criteria, there is a 58% probability of a Go decision and 13% probability of a Stop decision if the true ORR is 40%, and there is a 23% probability of a Go decision and 42% probability of a Stop decision if the true ORR is 30%.

TNBC

Given a sample size of 15 patients in the triple negative breast cancer group, where TV=25% and LRV=15%, the decision

criteria are as follows: Go if ≥ 4 responses observed (27%); Stop if ≤ 1 responses observed (7%). With these criteria, there is a 54% probability of a Go decision and 8% probability of a Stop decision if the true ORR is 25%, and there is a 18% probability of a Go decision and 32% probability of a Stop decision if the true ORR is 15%.

AML

The same sample size, TV, LRV, decision criteria, and probability statements as the TNBC group apply.

General Considerations

Data will be summarized and/or analyzed by cohort. Safety and demographic data will be summarized using standard tabulations and listings. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum value, and maximum value. Continuous variables may be summarized by a clinically relevant discretization, as appropriate. Categorical variables will be summarized using frequency counts and percentages. Time-to-event data will be summarized using the Kaplan-Meier method. All time to event endpoints are measured from day of enrollment (Day-2 pretreatment baseline visit). Where appropriate, 95% confidence intervals around point estimates will be presented, and estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, and 12-month rates), will be produced. Data will be provided in data listings.

Objective response rate will be reported with category counts, percentage and 95% confidence interval. Duration of response (DOR), TTR, and OS will be evaluated using Kaplan-Meier estimates and curves will be generated based on these estimates.

Date of Protocol Amendment:	12 April 2019

List of Abbreviations

Abbreviation	Definition
aa	amino acids
AE	adverse event
AGO-OVAR	Arbeitsgemeinschaft Gynaekologische Onkologie - Studiengruppe Ovarialkarzinom
allo-SCT	allogenic (hematopoietic) stem cell transplant
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APC	antigen-presenting cell
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration curve
BCG	Bacillus Calmette–Guérin
BICR	Blinded Independent Central Review
BM	bone marrow
BP	blood pressure
CBC	complete blood count
CBFB/MYH11	core-binding factor beta subunit/myosin heavy chain-11
cDNA	complementary deoxyribonucleic acid
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CML	chronic myeloid leukemia

Abbreviation	Definition
CNS	central nervous system
CR	complete remission, complete response (AML)
CR1	first complete remission (AML)
CR2	second complete remission (AML)
CRC	colorectal cancer
CrCl	creatinine clearance
CRi	CR with incomplete recovery of blood counts (AML) (encompasses the definition of CRp)
CRi/CRp	CR with incomplete recovery of blood counts or platelets (AML)
CRO	clinical research organization
CRp	CR with incomplete recovery of blood platelets (AML)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T-lymphocyte
CV	coefficient of variation
DFS	disease free survival
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DTH	delayed-type hypersensitivity testing

Abbreviation	Definition
ECG	electrocardiogram
ECI	Events of Clinical Interest
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EDTA	ethylene diamine tetra-acetic acid
EFS	event free survival
ELISPOT	enzyme-linked immunospot
ELN	European LeukemiaNet
EOT	end-of-treatment
ES-SCLC	extensive stage small cell lung cancer
FAS	full analysis set
FDA	Food and Drug Administration
FIR	First Interpretable Results
FISH	fluorescence in situ hybridization
FN	febrile neutropenia
FT3	free triiodothyronine
FT4	free thyroxine
GBM	glioblastoma multiforme
gBRCA mut	germline BRCA mutations
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate

Abbreviation	Definition
GM-CSF	granulocyte-macrophage colony-stimulating factor
GOG	Gynecologic Oncology Group (US)
GPS	galinpepimut-S
H	hour
HBsAg	hepatitis B surface antigen
HCV RNA	hepatitis C RNA
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agent
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
iCPD	iRECIST confirmed progressive disease
ICS	intracellular cytokine staining
ICU	intensive care unit
IDH1	isocitric dehydrogenase-1
IEC	independent ethics committee
IHC	immunohistochemical
ILD	Interstitial lung disease

Abbreviation	Definition
INR	International Normalized Ratio
IR	immune response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
IRR	infusion related reaction
IRS	immuno-reactive score
ISR	injection site reaction
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
LFS	leukemia-free survival
LRV	lower reference value
LSC	leukemic stem cell
mAb	monoclonal antibody
MCC	Moffitt Cancer Center
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MDSC	Myeloid-derived suppressor cell
MHC	major histocompatibility complex
mITT	modified intent-to-treat
MK-3475	pembrolizumab
MM	multiple myeloma

Abbreviation	Definition
MOA	mechanism of action
MPM	malignant pleural mesothelioma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRK	Merck & Co., Inc., Kenilworth, N.J., USA (known as MSD outside the United States and Canada)
MS	microsatellite
MSI	microsatellite instability
MSKCC	Memorial Sloan-Kettering Cancer Center
MSS	microsatellite stable
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
OvC	ovarian cancer
PARP	poly-ADP ribose polymerase
PB	peripheral blood
PCR	polymerase chain reaction

Abbreviation	Definition
PD	progressive disease
PD-1	programmed cell death receptor 1
PFS	progression-free survival
PK	pharmacokinetics
PD-L1	ligand to PD-1 receptor
PML-RAR-α	promyelocytic leukemia-retinoic acid receptor alpha
PPS	per-protocol set
PR	partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SCLC	small cell lung cancer
SCT	stem cell transplant
SD	standard deviation
SIM	Site Imaging Manual

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
SWFI	sterile water for injection
$T_{1/2}$	terminal elimination phase half-life
T1DM	Type 1 diabetes mellitus
T3	triiodothyronine
TAA	tumor-associated antigens
TAM	tumor-associated macrophage
TBX	tumoral biopsy samples
TEAE	treatment-emergent adverse event
T_{max}	time at which the highest drug concentration occurs
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TRAE	treatment related adverse events
Treg	T-regulatory cell
TSH	thyroid stimulating hormone
TTR	time to response
TV	target value
ULN	upper limit of normal
US	United States
USP	United State Pharmacopeia
WBC	white blood cell
WOCBP	woman of childbearing potential
WT1	Wilms tumor gene

1 Introduction

1.1 Galinpepimut-S Background

1.1.1. Preclinical and Pharmacological Background

The Wilms Tumor-1 (WT1) protein, the WT1 oncogene product, was first identified in childhood renal tumors, but has been found to be overexpressed in a high proportion of solid and hematological malignancies, while its expression is substantially void in most healthy adult tissues (Wagner et al, 2014). WT1 was originally identified by complementary deoxyribonucleic acid (cDNA) mapping to a region of chromosome 11p13. The WT1 cDNA encodes a protein of 575 amino acids (aa) in length, containing 4 Kruppel zinc fingers and exhibiting a complex pattern of alternative splicing, resulting in 4 different transcription factors (Haber et al, 1990; Hohenstein et al, 2016). Each WT1 protein isoform has different deoxyribonucleic acid (DNA) binding and transcriptional activities, and can positively or negatively regulate various genes involved in cellular proliferation, differentiation, apoptosis, organ development, and sex determination (Haber et al, 1991). WT1 is normally expressed in tissues of the mesodermal origin during embryogenesis, including the kidney, gonads, heart, mesothelium, and spleen (Oji et al, 1999; Sharnhorst et al, 1999). In normal adult human tissues, WT1 expression is limited to very low levels in the nuclei of normal CD34+ hematopoietic stem cells, myoepithelial progenitor cells, renal podocytes, injured myocardium, and some cells in the testis and ovary (Mundlos et al, 1993; Buckler et al, 1991; Fraizer et al, 1995). Although originally described as a tumor suppressor gene, the WT1 proteins appear to be involved in tumorigenesis as a bona fide oncogene (Keilhoz et al, 2005; Lindstedt, et al, 2014).

As WT1 is a transcription factor and is not expressed intact in the cell membrane, it has not been able to be targeted (druggable) with either small molecules or monoclonal antibodies (Toska et al, 2014). Nonetheless, the protein is processed by the proteasome in tumors and the derived peptides are presented in a major histocompatibility complex (MHC)-dependent manner on the cell surface. Furthermore, WT1 peptide fragments when administered as direct

immunogens (vaccines) are also taken up by antigen-presenting cells (APCs) and processed by the immunoproteasome for MHC-dependent presentation (Jiagirdar et al, 2016; Asemissen et al, 2006; Müller et al, 2003). The above features render WT1 a highly attractive target for immunotherapy (Oka et al, 2002; Oka et al, 2007). WT1 was ranked as the top cancer antigen by a working group organized by the National Cancer Institute (NCI) in 2009 (Cheever, et al, 2009). The strong expression of WT1 protein in assorted cancers, coupled with its proposed mechanism of antigenicity and induction of immune responses (both CD4 and CD8 [Chapuis et al, 2013; Dao et al, 2016; Tyler et al, 2013; Tyler and Koehne, 2013; Fujiki et al, 2008; Krug et al; 2010]; after direct immunization against WT1 in patients with assorted cancers), makes it a rational candidate for the development of specific immunotherapies, such as peptide vaccines (Van Driessche et al, 2012; Oka and Sugiyama, 2010; Oka et al 2009; Dao and Seheinbert, 2008). The WT1 antigen is one of the most widely expressed cancer antigens in multiple malignancies. It has been ranked by the NCI – National Institutes of Health (NIH) - as the top priority among cancer antigens for immunotherapy (Cheever MA, et al 2009). WT1 is overexpressed in numerous hematological malignancies, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and multiple myeloma (MM), as well as in many solid malignancies such as malignant pleural mesothelioma (MPM), gastrointestinal cancers, i.e., colorectal cancer (CRC), glioblastoma multiforme (GBM), triple-negative breast cancer (TNBC), ovarian cancer (OvC), small-cell lung cancer (SCLC); all in all WT1 is expressed in at least 50% of tumor pathology specimens in up to 25 assorted malignancies (Oji Y et al, 2003; Bejrananda T et al, 2010-2011; Inoue K, et al, 1997; Nakatsuka S-I et al, 2006; Provenzano E, et al, 2016; Narita M et al, 2010; Di Stasi A et al, 2015; Tyler EM and Koehne G. 2013; Babiak A et al, 2014; Menssen HDet al, 2000; Oji Yet al, 2016; Nakahara Y et al, 2004; Van Driessche Aet al, 2005).

Despite WT1's broad expression in assorted malignancies, due to its nature - an intracellular transcription factor localized in the cell nucleus, and as mentioned earlier- it has been 'un-druggable' via standard pharmacology approaches, such as small molecules or surface-acting macromolecules (such as monoclonal antibodies). Thus, immunotherapy approaches, such as

direct immunizers (such as peptide-based vaccines) emerged as an attractive pathway to therapeutically target this key protein (Brayer and Pinilla-Ibarz, 2013; Schwartz J et al, 2003; Oka Y et al, 2006; Van Driessche A et al, 2012). Because WT1 protein is a self-antigen, breaking tolerance is a potential problem for an effective treatment. When developing potential treatment candidates, a strategy in use at Memorial Sloan-Kettering Cancer Center (MSKCC) to circumvent the poor immunogenicity and potential tolerance of tumor-associated peptides is to design synthetic analog peptides that will be more immunogenic. Such peptide analogues could generate an immune response that not only recognizes the immunizing epitopes, but also cross-reacts with the original native peptides; this is known as a heteroclitic response. By using computer prediction analysis, a large number of synthetic peptides derived from WT1 protein sequences were designed in which single or double aa substitutions were introduced into the peptides at key human leukocyte antigen (HLA)-A*A0201 binding positions (Pinilla-Ibarz et al, 2006; Gomez-Nunez M et al, 2006). Peptides predicted to bind with high affinity to HLA-A*A0201 molecules were directly assayed for their ability to stabilize major histocompatibility complex class I A0201 molecules on the surface of antigen-transporting-deficient T2 cell lines. The new synthetic peptides stabilized major histocompatibility complex class I A0201 molecules better than native sequences. Avidly binding peptides were then assayed in an antigen-specific T-cell expansion in vitro system for the ability to elicit HLA-restricted, peptide-specific cytotoxic T-lymphocyte (CTL) responses using purified T cells from healthy donors. The synthetic analog peptides generated more effective immune responses than the native peptides. In addition, CD8+ T-cells stimulated with the new synthetic peptides displayed heteroclitic features and cross reacted with the native WT1 peptides and also were able to mediate peptide-specific cytotoxicity. Importantly, T-cells stimulated with the new synthetic peptides cross-reacted with the native WT1 peptide sequence and were able to destroy HLA-matched CML blasts (Pinilla-Ibarz J et al, 2000;). This validates the expression and possibility of killing tumors in this system. Other groups have validated the same native sequence in use as a target (Mailänder et al, 2004).

Synthetic peptides with longer WT1 sequences were also designed by modifying previously identified WT1 peptide segments and adding flanking aa segments. These peptides are capable of stimulating a CD4+ response, which is necessary for inducing long-term T-cell memory. They can induce a peptide-specific CD4+ response that can recognize WT1-positive tumor cells in multiple HLA-DRB1 settings. Using cross-priming experiments, it was shown that the WT1 peptide is presented on the surface of mesothelioma tumor cells and could be recognized by the T-cells stimulated by the individual WT1-DR peptides (May et al, 2007).

In order to broaden immunogenicity over a range of HLA subtypes, 4 WT1-derived peptides were chosen to combine into a mixture to be used as a direct immunizer. The current candidate product, now known as galinpepimut-S, contains 1 WT1 heteroclitic peptide to stimulate CD8 responses (WT1-A1), 2 longer WT1 native peptides to stimulate CD4 responses (WT1-427 long and WT1-331 long) and 1 longer heteroclitic peptide that could stimulate both CD4 and CD8 cells (WT1-122A1 long). Galinpepimut-S, along with the immunological adjuvant Montanide™ with granulocyte-macrophage colony-stimulating factor (GM-CSF) pre-stimulation was then taken into human trials, initially in AML and mesothelioma, and subsequently in other indications (multiple myeloma and ovarian cancer).

With regard to the use of GM-CSF as an immune adjuvant and to establish the paucity of any confounding immunologic and/or clinical effects thereof when co-administered with galinpepimut-S, the following information is of relevance: Firstly, GM-CSF has been recognized as an activator of the first step in adaptive immunity responses to antigens, especially peptide vaccines over the last 25 years (Caux et al, 1996). Pre-stimulation of host macrophages/monocytes and other antigen-presenting cells (APCs) is absolutely required for the induction immune responses against moieties of relatively low antigenic potential (such as tumor-associated antigens, or TAAs) presented through the MHC Class I and II systems (Mach et al, 2000; Olatunde et al, 2018). This is true for oligopeptide fragments of the WT1 protein, including those within the galinpepimut-S tetravalent mixture. In essence, in order for most peptide vaccines to induce immunogenicity – leading to CD8+ and/or CD4+

lymphocyte activation, which is the prerequisite for the emergence of an immunologically mediated antitumor clinical effect, they need to be co-administered with an immune adjuvant. In a wide variety of such vaccines, including galinpepimut-S, one of the most commonly used (and more widely studied) adjuvant for this purpose is GM-CSF. Secondly, several clinical and immunobiological studies have shown lack of consistent effect of GM-CSF monotherapy, i.e., when this adjuvant is administered by itself and in the absence of another tumor-directed immunotherapy, with regard to GM-CSF's ability to induce or maintain antigen-specific T- and B-cell immune responses and clinical effect in patients with various malignancies (O'Day et al, 2009; Greter et al, 2012; Lawson et al, 2015). Indeed, although GM-CSF monotherapy in cancer patients has been shown to exert various modulatory effects in the number/frequency and activation level of dendritic cells (DCs) and other immunocytes, none of these cell subpopulations have even been consistently shown to be specifically directed to/reactive against tumor-associated antigens. This is especially true when GM-CSF is used in small doses (such as that used in this study, 70 μg per administration - rather than the per-label dose of 250 μg per administration) (Parmiani et al, 2007). Of note, in an earlier phase 2b, double-blinded, randomized, controlled clinical study of galinpepimut-S (plus GM-CSF) versus GM-CSF alone given in the maintenance setting after frontline debulking multimodality therapy in patients with malignant pleural mesothelioma, no WT1 (antigen)-specific T-cell (CD8 or CD4) immune responses were observed in the control arm. Further, the clinical outcome (as measured by overall survival since randomization) in the control arm was comparable to that reported in patients who relapsed during follow up for the natural history of their disease (Zauderer et al, 2017). Therefore, when all the above is taken into consideration, GM-CSF alone appears to be inactive with regard to antigen-specific immunogenicity and antitumor effect.

1.1.1.2. Justification for Galinpepimut-S Dose

A dose of 200 μg for each WT1 peptide within the galinpepimut-S mixture (total weight of all 4 peptides per inoculation being equal to 800 μg) was chosen because it is within the range of safe and active doses used in other WT1-based treatments. Peptide vaccines have

generated immune and clinical responses within a wide range of doses (100 to 2000 µg injected) without clear evidence of dose response relationships. Higher doses have the theoretical possibility of stimulating lower affinity T-cell receptors on T cells and reducing the response.

1.1.2. Galinpepimut-S Clinical Studies1.1.2.1. Phase 1 Clinical Experience with Galinpepimut-S (Study 06-085)

The MSKCC conducted a single institution, open-label, single arm Phase 1 study (#06-085) in patients with AML, non-small cell lung cancer (NSCLC), or mesothelioma to determine the safety and immunogenicity of treatment with galinpepimut-S (Krug et al, 2010; Maslak et al, 2010; ClinicalTrials.gov identifier: NCT00398138). Patients with myelodysplastic syndrome (MDS) were eligible to enroll in this study; however, none were treated. In this study, all HLA subtypes were eligible. Patients with AML were ≥ 65 years of age and had previously completed induction chemotherapy, achieved clinical remission, and completed postremission therapy, or completed induction chemotherapy, achieved clinical remission, and had no plans for further postremission therapy. AML patients had documented WT1-positive disease as demonstrated by WT1 protein on a pretreatment bone marrow (BM) biopsy or detectable disease with real-time quantitative reverse transcription polymerase chain reaction (RT-PCR). Mesothelioma patients were required to have malignant pleural mesothelioma or peritoneal mesothelioma, unresectable or relapsed disease, and had to have received no more than 1 prior pemetrexed-containing chemotherapy regimen. Patients with NSCLC were either stage III or IV and had completed initial treatment with surgery and/or chemotherapy and/or radiation therapy. Both mesothelioma and NSCLC patients were required to have neoplasms that showed immunohistochemical (IHC) staining for WT1 in greater than 10% of cells. Patients were stratified according to disease type: AML (Myeloid Group) versus NSCLC or mesothelioma (Thoracic Group). Results from the myeloid group are presented in the following sections. Results from the thoracic group can be found in the Galinpepimut-S Investigator Brochure v2.0, June 2017.

Galinpepimut-S as a *pharmaceutical preparation* is a multicomponent direct immunogen mixture, consisting of the 4 WT1 peptides defining the galinpepimut-S *drug substance* suspended in Montanide adjuvant. Sargramostim (hereafter referred to as GM-CSF) was administered at the injection site before each treatment. Treatment was administered on Weeks 0, 4, 6, 8, 10, and 12 for a total of 6 injections. Patients who had a clinical, molecular, or immunologic response and did not have disease progression were able to receive up to 6 additional administrations administered approximately 1 administration every month for 6 months.

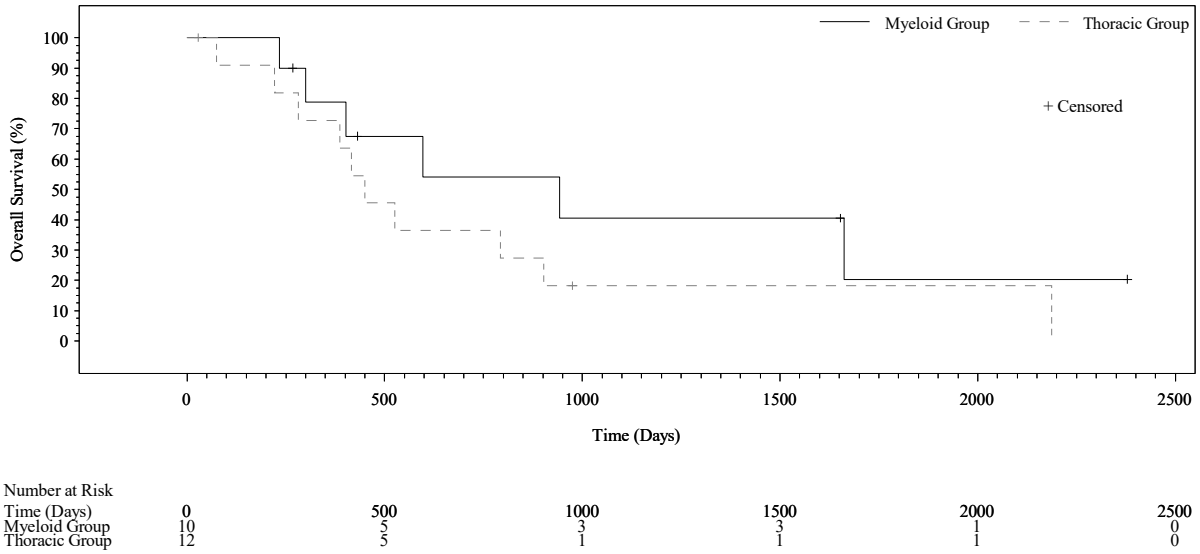
Ten patients were enrolled in the AML arm. Seven patients (70.0%) prematurely discontinued; the most frequently reported primary reason for discontinuing active treatment was progressive disease/disease relapse (4 patients). The remaining patients discontinued to the following reasons: 1 patient due to excessive toxicity, 1 patient due to another complicating disease, and 1 due to other reasons. The median age of patients was 67 years (range: 24 to 78 years). Seven patients (70.0%) were male and 3 patients (30.0%) were female.

In the myeloid group, all 10 patients received at least 1 administration with WT1 peptide. Eight patients (80.0%) received ≥6 administrations, and 5 patients (50.0%) received > 8 administrations. The total exposure to WT1 peptide ranged from 28 to 295 days, with a median of 144.5 days.

With regard to safety, in the myeloid group, hyperglycemia (10 patients; 100.0%) was the most common treatment-emergent adverse event (TEAE), followed by platelet count (8 patients; 80.0%); hemoglobin and white blood cell disorder (6 patients each; 60.0%); and hepatic enzyme abnormal, white blood cell analysis, and hypernatremia (5 patients each; 50.0%). Eight study treatment-related TEAEs were reported in 3 patients (30.0%) and were mild (all were ≤ Grade 2). The study treatment-related TEAEs were edema peripheral, erythema multiforme, injection site extravasation, platelet count, pruritus, white blood cell disorder, and white blood cell analysis. No serious TEAEs were reported in the myeloid group.

Four patients (40.0%) in the myeloid group were known to be alive with no progression of disease at the time of last contact and 6 patients (60.0%) died. The median overall survival (OS) in the myeloid group was 31 months (2.6 years; see Figure 1). One patient who received 7 treatments with galinpepimut-S was still alive as of Month 54.3 (4.5 years); another patient who received 8 treatments with galinpepimut-S was still alive as of Month 78.2 (6.5 years). Another patient, after completion of at least 12 treatments, had no progression of disease at the time of her death, on Month 54.6 (4.6 years).

Figure 1 Kaplan-Meier Plot for Overall Survival by Disease Group



The results from the myeloid arm of this Phase 1 study were superior to published AML outcome data (Ries et al, 2007; Appelbaum et al, 2006; Deschler and Lübbert 2006). Age appears to be a major determinant in patient outcomes, with the oldest populations deriving little benefit from many of the dose-intensive therapies introduced in the last few years. Appelbaum et al (2006) reported a median OS of 18.8 months in patients younger than 56 years of age, 9.0 months in patients 56 to 65 years of age, and 6.9 months in patients 66 to

75 years of age (Appelbaum et al, 2006). The median age of AML patients treated in the Phase 1 pilot study was 67 years of age; therefore, the outcomes for this study's AML group compare favorably with published data from Appelbaum et al where the youngest cohorts had the best outcomes. Though caution needs to be exercised in interpreting these results as there may be a bias regarding patient selection and reduced sample size in the study group, the results were intriguing enough to warrant further study in a larger clinical study examining the role of galinpepimut-S administration as a viable treatment for AML in complete remission status. Hence, additional Phase 2 studies were undertaken at the MSKCC.

1.1.2.2. Phase 2 Clinical Experience with Galinpepimut-SFour additional studies with galinpepimut-S were initiated at the MSKCC (A Phase 2 study in AML and acute lymphoblastic leukemia, a Phase 2 study in MPM, a Phase 1/2 pilot study in patients with multiple myeloma (MM), and a Phase 1/pilot study in ovarian cancer [OvC]). One additional Phase 1/2/pilot study was performed at the Moffitt Cancer Center (MCC) in patients with AML. Results from the Phase 1 and Phase 2 studies in AML and Phase 1/pilot study in OvC are discussed in the following section, as they are pertinent to 2 of the arms in the present study, while results from the other 2 studies (in MPM and MM) can be found in the galinpepimut-S investigator's brochure (IB). While not all primary endpoint data for all above studies have been reached, their preliminary results extend the observations from the the earlier trials and form the basis to investigate galinpepimut-S efficacy in randomized Phase 3 clinical trials of galinpepimut-S (given in the maintenance setting) in both AML and MPM after initial debulking therapy.

1.1.2.2.1. Study 10-143 (AML Patients)This open-label, Phase 2 trial (Maslak et al, 2018; ClinicalTrials.gov identifier: NCT01266083) evaluated the safety and efficacy (as measured by OS at 3 years) of galinpepimut-S used as postremission therapy in patients in complete remission (CR) from leukemia. In addition, this study assessed disease-free survival at 3 years, immunologic responses (as measured by CD4+ T-cell proliferation, CD3+ T-cell interferon-γ release, and WT1 peptide tetramer staining), and any effect the galinpepimut-S

had on minimal residual disease (MRD) (as measured by RT-PCR for WT1 transcript). Eligible patients were ≥18 years of age, had a morphological confirmation of a diagnosis of AML or acute lymphoblastic leukemia, and had achieved CR (within 2 years of first treatment administration) after completing induction therapy and any planned post-remission therapy. In addition, eligible patients could not be candidates for allogeneic stem cell transplantation. Potential patients who were ≥ 60 years of age, who achieved CR (within 2 years of first treatment administration) and in whom no further postremission chemotherapy was planned were eligible for enrollment. Eligible patients had documented WT1-positive disease, defined as the detectable presence of any WT1 transcript via RT-PCR on a BM performed at the MSKCC within 4 weeks before the administration of the first dose of treatment. At least 4 weeks must have elapsed between the patient's last chemotherapy or radiation treatment and the first administration. In this trial, patients were administered the treatment, prepared as an emulsion of galinpepimut-S and Montanide, every 2 weeks for a total of 6 administrations. Those who were clinically stable and without disease recurrence could continue with up to 6 more treatments administered approximately every month. All patients receive sargramostim (GM-CSF, 70 μg) administered subcutaneously 2 days prior to each treatment as well as on the actual day of each administration to prestimulate the injection site.

The data cut-off date for the disposition, demographic, and safety information was 22 May 2015; the data cut-off date for patient survival was 30 October 2015. As of the data cut-off date, 22 patients had been enrolled. No additional patients were enrolled, as the study has been closed to enrollment.

A total of 22 patients (7 men and 15 women) were enrolled on the study, were treated, and were evaluable for response. The median age was 64 years (range 25 to 76 years). Fifty percent (11 of 22) of study patients had a normal karyotype.

Of the 22 patients enrolled, 14 (64%) received the planned 6 galinpepimut-S administrations and 10 (46%) completed all 12 galinpepimut-S administrations. Overall, 15 (68%) patients relapsed: 10 while receiving treatment, 4 after the entire series of 12 galinpepimut-S

administrations, and 1 patient 13 months following discontinuation of therapy secondary to a delayed- type hypersensitivity reaction. Four of the 15 patients relapsed after 1 galinpepimut-S administration, likely an insufficient amount of time to induce an immune response. Ten relapsed patients died due to complications from progressive leukemia. Five of the 15 relapsed patients underwent hematopoetic stems cell transplant (HSCT) following successful re-induction chemotherapy. Three of these patients remained alive without evidence of recurrent disease, ranging from 11 to 31 months post-HSCT. There was no statistically significant difference in either relapse rate or OS in patients who were treated prior to spending 8 months in first complete remission (CR1) compared with those treated at or after this timepoint.

From first galinpepimut-S administrations, 19 of 22 (86%) patients were evaluable for survival at 3 years, and 9 of these 19 (47%) evaluable patients were alive for ≥3 years. Consequently, the study met its prespecified endpoint of ≥34% OS at 3 years.

From CR1, the median disease-free survival (DFS) was 16.9 months (Figure 2). The median OS from diagnosis (Figure 3) was not reached but is poised to reach or exceed 67.6 months (5.6 years by log-rank analysis). The median event free survival (EFS) from the time of first galinpepimut-S administration was 9.4 months, while the median OS from the time of administration has not been reached (Figure 4 and Figure 5). The probabilities of EFS at 6 and 9 months post galinpepimut-S administration were 64% (CI: 40%, 80%) and 54% (CI: 32%, 72%), respectively. Likewise, the probabilities of OS at 6 and 9 months post galinpepimut-S administration were 100% (CI: 100%, 100%) and 77% (CI: 54%, 90%), respectively.

For patients <60 years of age (n=9), neither the median DFS nor OS times were reached (Figure 6 and Figure 7). However, for patients in the older cohort (age >60; n=13), median DFS from CR1 was 10.8 months and median OS time post- diagnosis was 35.8 months (Figure 8 and Figure 9). Likewise, from first galinpepimut-S treatment, median EFS and OS times in the older cohort were 7.8 and 30.2 months, respectively. Lastly, landmark EFS in the older cohort at 6 and 9 months post first galinpepimut-S treatment were 54% (CI: 25%, 76%)

and 46% (CI: 19%,70%), respectively, while OS 6 and 9 months post first galinpepimut-S were 100% (CI: 100%,100%) and 62% (CI: 31%,82%).

Figure 2 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Disease-Free Survival**

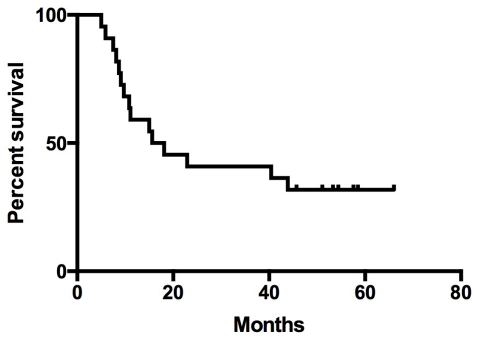


Figure 3 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Overall Survival**

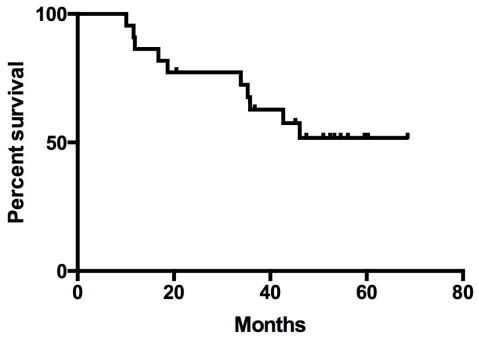


Figure 4 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median EFS from First Galinpepimut-S Administration**

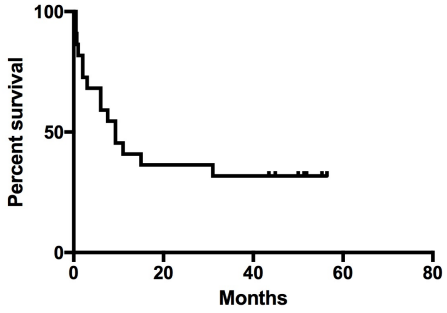


Figure 5 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Overall Survival from First Galinpepimut-S Administration**

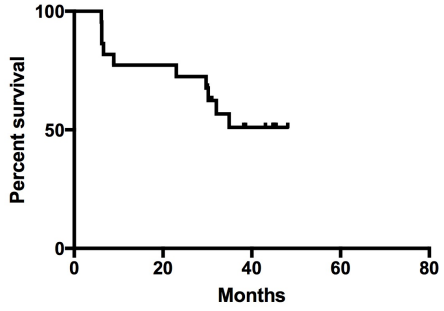


Figure 6 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Disease-Free Survival of Patients < 60 Years of Age**

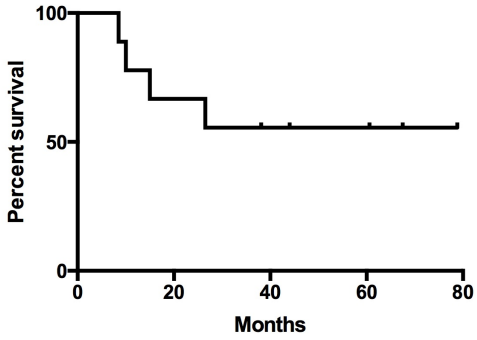


Figure 7 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Overall Survival of Patients < 60 Years of Age**

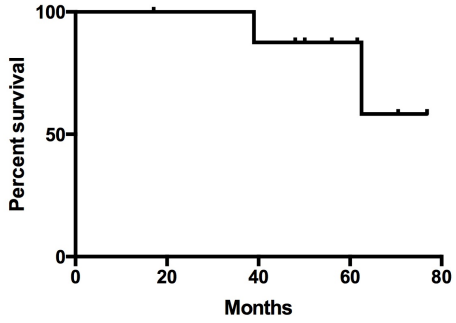


Figure 8 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Disease-Free Survival of Patients ≥ 60 Years of Age**

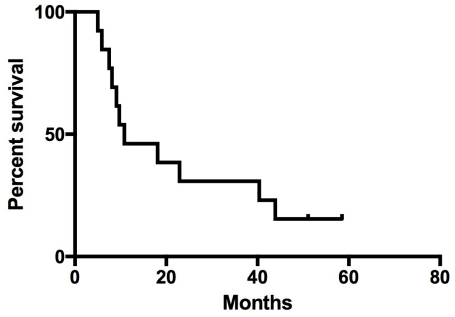
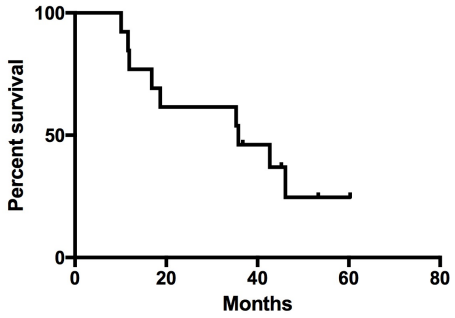


Figure 9 **Study 10-143 (AML Patients): Kaplan-Meier Plot for Median Overall Survival of Patients ≥ 60 Years of Age**



Galinpepimut-S administration was generally well tolerated and the toxicity profile is consistent with other WT1 vaccine-adjuvant combinations (Oka, et al, 2004; Keilholz et al, 2009; Rezvani et al, 2008; Rezvani et al, 2011; Uttenthal et al, 2014). The montanide adjuvant is a known irritant (van Doorn et al, 2015) and many of the most frequent toxicities consisted of mild to moderate local reactions and inflammation: injection site reaction (46%), fatigue (32%), skin induration (32%), and injection site pruritus (27%). These toxicities were self-limited and responded to local supportive measures and analgesics. Several transient occurrences of decreased white blood cell, neutrophil, lymphocyte, and platelet counts were noted and these resolved, often on the same day of testing, and resulted in no significant

infectious complications or supportive transfusions. None of the patients developed significant hepatic or renal insufficiency and no episodes of systemic anaphylaxis were observed.

Overall, galinpepimut-S in this population of AML patients was safe and well tolerated, with a majority of TEAEs being of mild or moderate severity (150/244, 61.5%). There were no reported deaths and a majority of Grade 3/4 TEAEs were unrelated to study treatment. The majority of injection site reactions, skin induration, and pruritus were easily managed with supportive care. Two patients discontinued therapy due to probable hypersensitivity reactions that were believed to be related to study treatment. One patient developed 2 episodes of a maculopapular rash (Grade 1) and then developed, on a separate occasion, an episode of flushing (Grade 3) immediately following the second study treatment administration. The patient remained hemodynamically stable and developed no signs of anaphylaxis but, given the severity of the episode, he discontinued further treatment. The patient subsequently relapsed and died from complications of recurrent AML 29 months after discontinuing galinpepimut-S treatment. The second patient developed bone pain, dyspnea, flushing, and non-cardiac chest pain (Grade 3) leading to hospitalization immediately following the fourth administration. The patient responded to standard supportive measures and the symptoms resolved the same day without further incident. The patient recovered without sequelae and remains alive as of the last study follow-up (approximately 36 months after discontinuing galinpepimut-S).

Although this is a relatively small study (22 patients), several clinical observations regarding the potential for therapeutic efficacy can be made. The study met its pre-specified endpoint of ≥34% actual OS rate at 3 years. The actual OS rate of 47.4% at 3 years post galinpepimut-S administration exceeded historical published data of 20-25% by 2.4-1.9-fold (or 240% to 190%), respectively. In addition, 11 of the 22 (50%) patients were alive at the time of their last assessment. Nine of these remained in CR1, while 3 relapsed during or following galinpepimut-S administration and were successfully salvaged with HSCT. The median DFS from CR1 was 16.9 months, with the median OS not reached, but poised to be at

least 67.6 months. These survival outcomes are higher than published results for similar patients treated with conventional post-remission therapies and compare favorably to subsets of patients treated with HSCT (Lowenberg et al, 2009; Fernandez et al, 2009; Kolitz et al, 2010; Nand et al, 2013; Dombret et al, 2015; McClune et al, 2010; Saber et al, 2012; Walter et al, 2010; Yanada et al, 2007).

However, there are several potential caveats in interpreting the results of this study with regard to therapeutic efficacy. The study population is relatively heterogeneous with several different prognostic groups contained within the data set which could skew outcomes (Rollig et al, 2011). The patients enrolled in this study may represent those with the best possible response in that not only were they able to achieve CR1, they remained in CR1 for a median of 8 months prior to treatment with galinpepimut-S. The immunologic correlates provide information regarding biologic effect but are not surrogates for clinical response. Several patients did not exhibit an immune response, yet still did well. We do not know if the patients that were negative were false negatives, as the assays are not sensitive, nor directed at most relevant key epitopes, nor are all technical issues regarding testing of this type resolved to date (Butterfield, 2015).

Despite these potentially confounding factors, this study supports the continued investigation of galinpepimut-S as a strategy for AML postremission therapy. Galinpepimut-S can be administered on an outpatient basis with minimal toxicity in most patients. This cohort of patients appears to do well compared with historical outcome data and the immunologic correlates which have been used in this study show the generation of an immune response in most tested patients.

1.1.2.2.2. Study MCC-15025 (AML Patients)

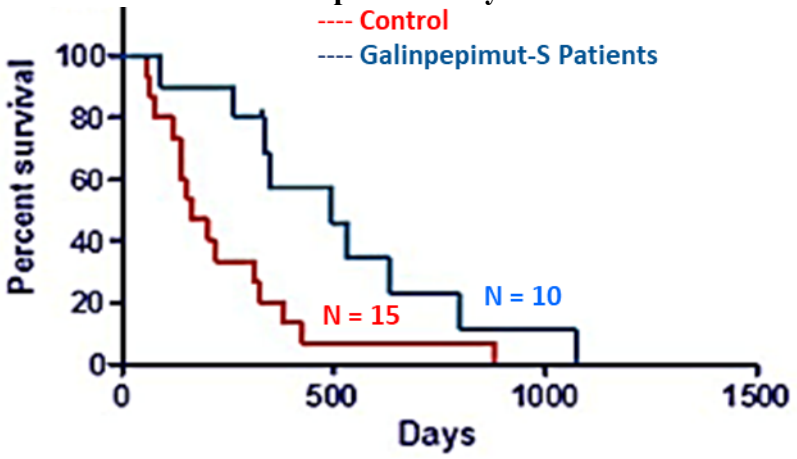
Galinpepimut-S was studied at the same dose, schedule, and overall manner of administration as in the previously discussed studies has been used in only 1 other known study in patients with AML. In 2015, Brayer et al published the findings of a study conducted at the Moffitt Cancer Center (MCC) that enrolled patients with either WT1-positive AML in CR1

or second complete remission (CR2), or MDS following at least 1 prior line of therapy (Brayer et al, 2015; ClinicalTrials.gov identifier: NCT00665002). Patients enrolled in the study received galinpepimut-S, along with GM-CSF on Days -2 and 0 of each galinpepimut-S dose. Patients received 6 bi-weekly galinpepimut-S administrations, and continued monthly until they had received 12 doses in total or showed evidence of disease relapse. Patients were evaluated for overall survival and progression free survival (PFS) from the time of the last remission, and immune response was evaluated by delayed-type hypersensitivity testing (DTH) and T cell interferon-γ enzyme-linked immunospot (ELISPOT) assay at specific intervals. The key findings of this study pertain to the subgroup of patients with AML who successfully achieved CR2 after 2nd line standard antileukemic therapy, and more specifically a cohort of 10 patients who received >2 galinpepimut-S inoculations and therefore had adequate exposure to the vaccine so that they could become immunized. The clinical outcomes (PFS and OS) in these patients were compared to post-hoc matched, contemporaneously treated patients with AML in CR2 status, a cohort that was used for 'historical' controls in the comparison.In more detail, a total of sixteen (16) patients (2 with refractory MDS and 14 with AML [4 in first CR and 10 in second CR]) were enrolled in the study. Five of the 14 AML patients had a prior diagnosis of MDS or myeloproliferative neoplasm. Nine of the 14 AML patients and both of the MDS patients exhibited a normal karyotype on cytogenetic analysis of the BM. Of the 5 AML patients with abnormal karyotype at baseline, 3 had complex karyotype, 1 contained a t (15;17) translocation not involving the classic promyelocytic leukemia-retinoic acid receptor alpha (PML-RAR-α) translocation, and 1 contained a core-binding factor beta subunit-myosin heavy chain 11 (CBFB/MYH11) (inversion 16) translocation (Brayer et al, 2015). The median age of patients was 74 years. Of the 16 patients, 9 completed the planned 6 galinpepimut-S doses, and 6 continued for up to 6 additional doses. Of the 14 patients with AML, 10 received >2 inoculations of galinpepimut-S and were eligible for formal PFS and OS endpoint analysis. Out of these 10, 4 completed a total of 12 galinpepimut-S doses while all other AML patients discontinued this agent due to disease progression. Of the 2 patients with MDS, 1 completed the planned 6 galinpepimut-S doses and went on to receive a total of 10 doses.

The remaining patient received 4 galinpepimut-S doses but discontinued due to progressive disease with transformation to AML.

For the patients with AML, the mean time to disease progression (AML relapse) was 8.0 months and the mean OS from time of CRs was 19.9 months (range 6.6 to 35.2 months). At the time of the published study manuscript in 2015, (Brayer, et al, 2015), 11 of the 14 patients had died and 3 remained alive but with progressive disease. Four of the 14 patients had sustained responses either equaling or exceeding the time period of their initial remission. An ad hoc analysis comparing the outcomes of 10 eligible AML patients in CR2 enrolled in the study who received >2 inoculations of galinpepimut-S with those of a contemporaneously treated historical matched cohort (n=15) demonstrated a numerical difference in median PFS (10.5 months versus 4.3 months; P = 0.19) in patients treated with study drug, but demonstrated a statistically significant and clinically meaningful improvement in median OS in the same comparison in favor of the active arm (16.3 months versus 5.4 months, P = 0.0175). These data are shown in Fig. 10 below:

Figure 10 Study MCC-15025 (AML Patients in CR2): K-M Plot for Median OS in Galinpepimut-S-treated pts who Received >2 Vaccine Inoculations (N=10) versus Contemporaneously Treated Historical Matched Controls (N=15)



Both MDS patients remained transfusion-dependent but 1 patient demonstrated a 50% reduction in the need for transfusion as compared to the 4 months prior to enrollment. An analysis of the patient's BM

showed an approximately 40% reduction in myeloblast percentage. The second patient demonstrated no response while receiving galinpepimut-S treatment but became transfusion-independent after study completion and had remained so for over 14 months prior to publication of the manuscript.

Four of the 14 AML patients developed a DTH response, while neither of the MDS patients did. An interferon-γ response by CD4 T cells was observed in 4 patients, with 3 of these patients also demonstrating CD8 T-cell-mediated interferon-γ responses.

Galinpepimut-S was well tolerated, with most AEs reported as Grades 1 or 2. There was a single Grade 3/4 AE of neutropenia. Six of the 14 patients experienced injection site reactions. Two of these patients developed local induration and erythema after completion of the protocol; both developed delayed-type hypersensitivity responses.

Note: As galinpepimut-S is always co-administered with the light oil Montanide in the form of an emulsion, as will be the case in this study, specific information about this emulsifying agent is provided in the Montanide Investigator Brochure.

Note: As patients will be administered SC sargramostim (GM-CSF) at the site of the planned galinpepimut-S injection 2 days before (Day –2) and the day of (Day 1) each injection of galinpepimut-S (emulsified in Montanide), specific information about sargramostim (GM-CSF) is provided in the US Prescribing Information for Leukine®.

1.1.2.2.3. Study 15-247 (Ovarian Cancer Patients)

Galinpepimut-S was studied a phase 1 single-arm trial at MSKCC to evaluate its safety and immunogenicity in combination with the PD1 inhibitor nivolumab (Opdivo®; Bristol-Myers Squibb) in patients with WT1(+) ovarian cancer in second or greater remission after successful debulking with standard chemotherapy. The preliminary results were reported in 2018 (O'Cearbhaill et al, 2018; ClinicalTrials.gov identifier: NCT02737787).

Patients were enrolled from June 2016 to July 2017, and received 6 galinpepimut-S inoculations over a period of 12 weeks (on weeks 0, 2, 4, 6, 8 and 10). GM-CSF (70 μg) was administered 2 days prior to and on the day of each vaccine administration. All galinpepimut-S inoculations were administered subcutaneously in extremities, with rotation of the injection site with each vaccination. Nivolumab at a dose of 3mg/kg per administration was given IV q 2weeks over 12 weeks. Patients who remained in remission were offered a maintenance course of galinpepimut-S at weeks 19, 27, 35, 43. Dose modification was not permitted. Treatment was continued until disease progression (assessed by RECIST 1.1) or toxicity (assessed by NCI CTCAE v4.03). The primary endpoint is to evaluate the safety of the combination. Dose limiting toxicity (DLT) was defined as an adverse event (AE) at least possibly related to the galinpepimut-S plus nivolumab combination occurring with 30 days from the 1st galinpepimut-S administration, and included (among other criteria) grade 2 uveitis, grade 3 injection site reaction, grade 3 fever, grade 3 AEs lasting >72 hours, grade 4 AE's (with the exception of clinically non-significant lab toxicities) or grade 5 AEs. Detection of greater than 2 DLTs among 10 treated patients would have deem the combination unsafe, but this was not observed. An exploratory objective was the progression-free survival (PFS) landmark rate at 1-year. PFS was measured from the start date of the immediately preceding chemotherapy to the date of progression of disease or death.

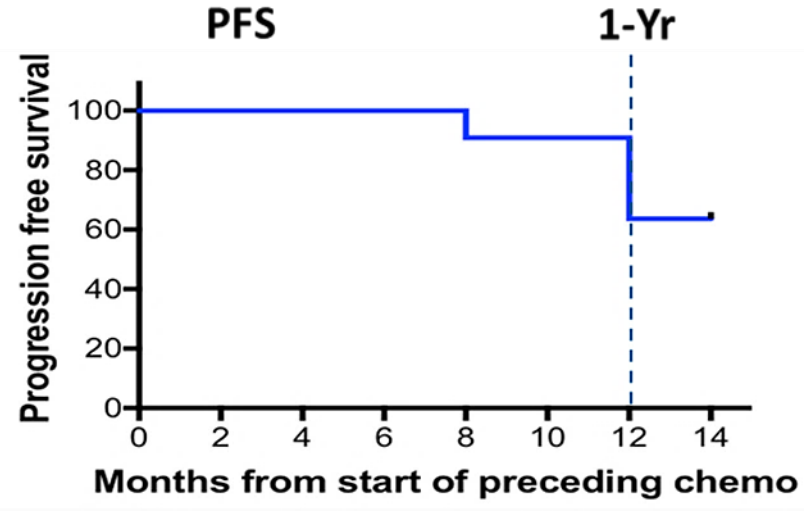
IgM & IgG antibody (Ab) responses were measured by ELISA against individual WT1 peptides contained within the galinpepimut-S mixture, as well as full length WT1. Immune responders were defined as those with Ab titers going from undetectable to ≥1:40 or ≥8-fold increase if such patients had detectable pretreatment levels. WT1-specific CD4+ and CD8+ T cell responses were compared to baseline via intracellular cytokine staining flow cytometry and values ≥0.6% were considered positive.

Eleven patients with recurrent serous ovarian cancer in their 2nd or 3rd remission were treated on-protocol with the combination of galinpepimut-S and nivolumab. Their baseline demographics and disease characteristics were representative of similar cohorts of patients in

the published literature - mainly by the Gynecologic Oncology Group (GOG) in the US and the Arbeitsgemeinschaft Gynaekologische Onkologie - Studiengruppe Ovarialkarzinom (AGO-OVAR) in Germany. The most common treatment-related AEs with the combination were injection site reaction (maximum [max] grade 1), arthralgia (max grade 2) and fatigue (max grade 2). DLT was observed in one patient, who developed grade 3 panmyositis (including cardiac involvement) following the 2nd dose of galinpepimut-S and nivolumab and required insertion of a permanent cardiac pacemaker. With regard to immune responses, serum levels of antigen-specific IgG, against both individual WT1 peptides within galinpepimut-S and the full-length WT1 protein were induced in 86% of evaluable patients between week 6 and week 27 following treatment with the combination. Antigen-specific T cell responses to individual WT1 peptides were observed between weeks 6-15. These responses were primarily CD4+, with best responses seen against the heteroclitic peptide 122A1-Long and its corresponding native counterpart 122A-Long, and to a lesser extent CD8+, mainly for peptides 427 and 331 in patients with HLA class I allelic types other than HLA-A02.

The landmark PFS rate at 1-year was 64% in the intent-to-treat group as shown in Figure 11 below. The 1-year PFS rate was 70% for patients who received >2 doses of galinpepimut-S and nivolumab.

Figure 11 **Study 15-247 (Ovarian Cancer Patients): Kaplan-Meier Plot for Median Progression-Free Survival Showing the Landmark 1-year PFS Rate in the ITT Population**



This Phase 1/Pilot study concluded that administration of the immune-targeted combination of the subcutaneously inoculated galinpepimut-S vaccine and the intravenous anti-PD1 agent nivolumab to patients with WT1-positive ovarian cancer in second or third remission was safe and well tolerated and resulted in high rates of antigen-specific immunization. Furthermore, the landmark PFS rate of 70% in patients who received >2 doses of the combination (N=9) compares favorably to historic rates that do not exceed approximately 50% in comparable populations treated with chemotherapy regimens that are currently considered standard of care (but without post-chemotherapy maintenance). The findings suggested that the combination of galinpepimut-S and anti-PD1 antibodies warrants further evaluation in patients with WT1-positive ovarian cancer, and provides strong background rationale for the launch of the ovarian cancer arm in the present study.

1.2 Pembrolizumab Background

1.2.1. General

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (edition 16.0, dated 29 June 2018).

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

1.2.2. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al, 2005; Hunder et al, 2008).

The 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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) (Greenwald et al, 2005; Okazaki et al, 2001).

The structure of murine PD-1 has been resolved (Zhang et al, 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki et al, 2001; Chemnitz et al, 2004; Sheppard et al, 2004; Riley, 2009). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry et al, 2005; Francisco, 2010). As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in the 5 malignancy types investigated in this study.

1.2.3. Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano et al, 2005; Blank et al, 2004; Weber, 2010; Strome et al, 2003; Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010). Anti-mouse PD-1 or anti-mouse

PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome et al, 2003; Curran et al, 2010; Pilon-Thomas et al, 2010; Nomi et al, 2007; Zhang et al, 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran et al, 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Pembrolizumab Investigator's Brochure [I.B.]).

1.2.4. Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),

Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010,

and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

1.3. Study Rationale

1.3.1. General

There is clearly an unmet need for novel and effective therapy to improve responses and prolong disease remission/progression-free intervals already achieved with checkpoint

blockade monotherapy (Farkona et al, 2016). The objectives of the proposed clinical study are: (i). to explore clinical outcomes (safety and potentially promising activity) in tumors using a combination of agents that improve immune-mediated anticancer effects, namely, pembrolizumab and galinpepimut-S, and (ii). to maximize the chances of detecting a clinically meaningful efficacy signal in comparison to historical monotherapy data (with pembrolizumab alone) for further validation in larger, randomized trials.

The rationale behind this clinical study consists of 2 parts as detailed below.

1.3.1.1. Rationale for Galinpepimut-S and Pembrolizumab Combination Therapy

Immune activation, suggested by the presence of infiltrating cytotoxic T cells in tumors, as well as eventual maintenance of a long-term proimmune status against the tumor via memory T cells, have shown be associated with a better prognosis across a wide variety of malignancies (Reeves et al, 2017; Wölfl M et al, 2014). Therapies blocking programmed death receptor 1 (PD-1), such anti-PD-1 monoclonal antibodies, have shown the ability to reduce inhibitory immune signals within the tumor microenvironment (TME), thus allowing cytotoxic T cells to infiltrate the tumor and cause tumor regression in an expanding group of human malignancies, leading to a series of regulatory approvals and clinical usage on a global scale (Intlekofer et al, 2013; Kyi et al, 2014; Spranger et al, 2016). These advances notwithstanding, there is significant room for improvement in both the depth, frequency, and duration of antitumor responses with anti-PD1 agents. This provides a strong rationale for developing strategies to prime a host (cancer patient) with tumor-specific cytotoxic T cells targeted to specific tumor antigens via host administration while increasing the likelihood of significantly amplifying such a specific response with an anti-PD1 therapy (in this case, pembrolizumab), as well as prolong the duration of such a response (Perez-Gracia et al, 2014) by both mitigation of tolerance and via induction of memory T cells (Marzo et al, 2000). Thus, combining innovative, highly tolerable actively immunizing agents, such as peptide treatments against well-validated high-antigenicity tumor targets with anti-PD1

products, such as pembrolizumab (Keytruda®), represents a highly attractive strategy, which deserves assessment in the clinical setting (Parchment et al, 2016; Drake CG, 2012).

As mentioned previously, galinpepimut-S is a directly immunizing therapy (a vaccine-like proprietary mixture of carefully selected heteroclitic and native WT1 peptide fragments) proven to produce WT1-specific T-lymphocytes in patients that could target a patient's cancer (Gomez-Nunez et al, 2006; Pinilla-Ibarz et al, 2006; Bleakley and Ridell, 2011; May et al, 2007; Brayer and Pinilla-Ibarz, 2013). Additionally, galinpepimut-S monotherapy has previously shown promising clinical activity in both pilot and Phase 2 studies in patients with AML, MPM, MM and OvC; all data originating from studying the effects of galinpepimut-S in a MRD setting, i.e., in the absence of measurable/macroscopic disease burden (after initial debulking of the malignancy), whereby the potential influence of TME factors has been mitigated (Maslak et al, 2010; Krug et al, 2010; Brayer et al, 2015; Maslak et al, 2016; Maslak et al, 2018; Zauderer et al, 2016; Zauderer et al, (iMig), 2016; Zauderer et al, 2017; Koehne et al, 2017; http://e-materials.com/ebmt2017/#/presentation/16745; https://learningcenter.ehaweb.org/eha/2017/22nd/181028/guenther.koehne.wt1.heteroclitic.epitope.immunization.following.autologous.html; Koehne et al, 2018; O'Cearbhaill et al, 2018; Tsuboi et al; 2012).

Galinpepimut-S is generally well tolerated. In a total of 122 patients across multiple studies, TEAEs either clinical or laboratory-test-related (including those of Grade 3/Grade 4 severity) were due to the underlying disease processes or complications thereof. Treatment-related adverse events (TRAEs) included injection site reactions, skin induration, and pruritus occurred at a frequency of 43.8% to 62.5% across studies, and were Grade 1/Grade 2 in severity, consistent with the fact that Montanide (which is co-administered with galinpepimut-S) is a known irritant. All TRAEs observed with galinpepimut-S monotherapy were manageable and did not lead to study drug discontinuation, with the exception of 2 patients in the AML Phase 2 study, who discontinued therapy due to probable hypersensitivity reactions (not anaphylaxis) (SELLAS, Data on file; Maslak PG et al, 2018;

Zauderer et al, 2017; Koehne et al, 2017; O'Cearbhaill et al, 2018; Galinpepimut-S Investigator Brochure v2.0, 08 June 2017).

Therefore, combining galinpepimut-S with the checkpoint inhibitor pembrolizumab, which beneficially and profoundly alters the TME (among other potent immunostimulatory effects in the host), is hypothesized to increase the proportion of patients who develop an immune response against their cancer and potentially improve their clinical outcome over pembrolizumab monotherapy, without the burden of additional toxicities in macroscopically measurable malignancies.

In this clinical trial, for each chosen tumor type to be studied, we will investigate whether galinpepimut-S administered concomitantly with the well-characterized adjuvant Montanide (van Doorn et al, 2016; Montanide IB 2015; Aucouturier et al, 2002; Aucouturier et al, 2001; Tovey and Lallemand, 2010) (also with GM-CSF priming at Day -2 and Day 1 of galinpepimut-S administration) can be safely administered with pembrolizumab, as well as preliminarily assess the degree of efficacy of anti-PD1 monotherapy when considered in the context of historical controls, as assessed by overall response rate (ORR). Moreover, we will investigate various secondary and exploratory endpoints. For the latter, we postulate that galinpepimut-S will induce a WT1-specific immune response, which will be associated with enhancement of clinical benefit seen with pembrolizumab monotherapy alone. Additional secondary efficacy measures (such as duration of response), as well as exploratory endpoints including WT1-specific immune response dynamics, and overall survival, will be investigated. If this pilot study meets the primary efficacy endpoint of ORR for a given tumor type, a randomized Phase 2 trial would be warranted in that tumor type.

Finally, as mentioned previously, in Section 1.1.1. (titled: "Preclinical and Pharmacological Background" – for galinpepimut-S), it is important to note that GM-CSF alone appears to be inactive with regard to antigen-specific immunogenicity and antitumor effect, and, therefore, any immunobiological (as assessed by WT1-specific T-cell immune responses) or clinical (as measured by ORR – for solid tumors- or CR/CRi/CRp -for AML) synergy between

galinpepimut-S and pembrolizumab observed in this study would be solely attributable to the co-administration of these 2 experimental agents (and not GM-CSF).

1.3.1.2. Rationale for Selection of Indications

The tumor types selected for this trial have been documented to commonly express WT1, and this trial will select patients whose tumors are positive for WT1 expression (assessed by commercially available IHC methods using standard anti-WT1 antibodies in paraffin-embedded specimen sections).

The following [up to 5] tumor types will be included: CRC, OvC, SCLC, TNBC, and AML. The choice of these tumor types was based on specific features of each malignancy, as detailed below. For all solid tumor indications, the highest citable number of lines of therapy listed below is the maximum allowed for eligibility, i.e., patients who have received subsequent lines of therapy are ineligible.

1.3.1.2.1. Metastatic Colorectal Cancer (Third/Fourth line)

Colorectal cancer (CRC) is a common disease, diagnosed in nearly 1.4 million people worldwide annually (GLOBOCAN 2012). In the United States, there are nearly 133,000 new diagnoses each year (Key Statistics for Colorectal Cancer, 2016). Approximately one-third of patients with CRC will develop metastatic disease. In most of these patients, the disease relapses and becomes refractory. The overall prognosis of patients with metastatic CRC has improved significantly, with average survival today being 30 months (Formica and Roselli, 2015), thanks to new research identifying different molecular subtypes of CRC. Although some patients with metastatic CRC can be cured, the disease remains incurable in most cases, clearly indicating a need for new therapies.

WT-1 expression has been documented to be expressed in between 70 to 90% of patients with CRC (Miyata et al, 2007; Oji et al, 2003; Bejrananda et al, 2011). Patients with

microsatellite-stable (MSS) molecular genetics make up between 80 to 90% of all CRC cases (Naboush et al, 2017; Diaz and Le, 2015). In this study, patients will have microsatellite (MS) instability (MSI) status tested in their primary tumors and will be classified as MSI- high (H) and -low (L) (Pawlik et al, 2004; Morán et al, 2010; Supek and Lerner, 2015; Goldstein et al, 2014). The focus will be on MSI-low tumors, but no entry selection will be applied based on this tumor feature. In several clinical trials in MSI-L CRC, anti-PD-1 agents have shown to induce 0 to 5% ORR (Link and Overman, 2016; http://www.targetedonc.com/publications/targeted-therapies-cancer/2017/2017-february/immune-checkpoint-inhibitors-in-crc; Boland and Ma, 2017; Myint and Goel, 2017; Overman et al, 2016; Segal et al, 2016; Bendell et al, 2016; Overman et al, 2016; Andre et al, 2017). This is in contrast to the significant activity of PD1 blockade in MSI-H CRC, the basis for the recent Food and Drug administration (FDA) approval of pembrolizumab in MSI-H cancers (including CRC) (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm). Only those CRC patients with MSS and MSI-H will be included in the efficacy analyses.

In several clinical trials, anti-PD-1 agents have shown between 0 to 5% ORR in these patients. We plan to treat patients with metastatic CRC previously treated with at least 2 lines of prior systemic chemotherapy (third/fourth line population) (n = 20).

Expression of ligand to PD-1 receptor (PD-L1) is associated with poor prognosis in CRC and has been shown to promote invasion of CRC cells in vitro. Pembrolizumab is a highly selective, humanized monoclonal anti-PD-1 antibody designed to block the interaction between PD-1 and its ligands, thereby enhancing antitumor immune activity. Pembrolizumab monotherapy has an acceptable safety profile but minimal antitumor activity in patients with heavily pretreated PD-L1-positive advanced CRC (Bendel et al, (ESMO); Le et al NEJM; http://www.ecco-org.eu/Vienna2015/Scientific-Programme/Abstract-search?abstractid=21431 [KEYNOTE 028]) showing MSS molecular features. In view of the above, there is good rationale to investigator the combination of galinpepimut-S plus pembrolizumab in CRC-MSS.

1.3.1.2.2. Ovarian Cancer (Second/Third line)

OvC is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer death in women in the United States. Over 22,000 cases are diagnosed annually, and there are an estimated 15,500 deaths per year (Siegel R, et al 2012). The majority of patients have widespread disease at presentation (Hoskins WJ, et al 2005). The 5-year survival for advanced-stage disease remains less than 30% (Siegel R, et al 2012). Although a complete clinical remission following initial chemotherapy can be anticipated for many patients, a review of second-look laparotomy when it was often performed as a matter of routine care indicates that less than 50% of patients are actually free of disease (Barnhill DR, et al, 1984). Furthermore, nearly half of patients with a negative second look procedure relapse and require additional treatment (Rubin SC et al, 1988). Many patients will achieve a second complete clinical response with additional chemotherapy. However, almost all patients will relapse after a short remission interval of 9 to 11 months. (Markman M et al, 1991). Effective strategies to prolong remission or to prevent relapse are required (Hoskins WJ et al, 2005).

With regard to immunotherapy approaches in OvC, immunization against tumor-associated antigens (TAA) lead to emergence of both TAA-specific antibodies and T-cell effectors have been shown to provide benefit in OvC models. Antibodies have been noted to curtail early tissue invasion (Zhang H et al, 1998). Preclinical models have also demonstrated the clearance of circulating tumor cells and the elimination of systemic micrometastasis through the use of both passively administered and vaccine-induced antibodies. With regards to T-cell effectors, a globally activated immune response has been shown to be associated with improved clinical outcome in patients with advanced OvC. Zhang et al showed that the presence of tumor infiltrating T cells within tumor cell islets was associated with improvement in both progression free and OS (Zhang H et al, 2003). Conversely, the infiltration of T- regulatory cells confers a worse prognosis (Curiel TJ et al, 2004).

OvC patients in second or greater remission confirms them to relapse in a predictable fashion (Iasonos A et al, 2012) and, therefore, are candidates for novel immune-based

"consolidation" strategies, such as those including checkpoint inhibitors and TAA-directed immunizing vaccine-type therapies, like galinpepimut-S, either alone or in combination.

The strong expression of WT1 protein in OvC coupled with its proposed mechanism of action makes it a rational target for immunotherapy. WT1 expression is highly prevalent in OvC (Dupont et al, 2004). Indeed, WT1 expression is high enough that pathologists routinely use IHC stains for WT1 with a standardized convention for describing expression and determining as "positive" or "negative" to help distinguish epithelial ovarian cancers from other tumors (Al-Hussaini et al, 2004). WT1 is a particularly sensitive and specific marker for serous ovarian cancer (Acs et al, 2004). Ovarian tissue microarrays at MSKCC (New York, USA) suggest approximately 80% of serous ovarian cancers express WT1 (Lim et al, 2016), thus corroborating earlier studies with IHC (Tornos et al, 2005; Köbel et al, 2009; Karamurzin et al, 2013).

Overexpression of the PD-1 ligand PD-L1 has been demonstrated in OvC and may hinder an effective antitumor immune response (http://abstracts.asco.org/199/AbstView_199_184843.html). The activity of anti-PD1 agents in recurrent OvC in second and third lines of therapy is reflected in ORR values of approximately 15% (Varga et al, 2015; Weiss et al, 2017). In a previous clinical study with pembrolizumab with 15.5 months of follow-up, as well as in a review of the existing recent literature in the use of PD-1 blockers in OvC, pembrolizumab continued to be well tolerated and demonstrated durable antitumor activity in patients with advanced OvC (Mittica et al, 2016). In view of the above, there is good rationale to investigate the combination of galinpepimut-S plus pembrolizumab in OvC.

1.3.1.2.3. Small Cell Lung Cancer (Second Line)

Treatment options for patients with SCLC who progress on platinum-based chemotherapy are limited. WT1 expression has not been studied in SCLC as extensively as in NSCLC, mainly due to the relative rarity of the former. Nonetheless, WT1 positivity is higher (40 to 83%) in SCLC versus NSCLC (Babiak et al, 2014; Menssen et al, 2000; Oji et al, 2002;

Wang et al, 2013). Therefore, WT1 is an appropriate target for direct TAA-specific immunotherapy approaches, such as galinpepimut-S. Pembrolizumab, an anti–PD-1 monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2, has shown antitumor activity in multiple advanced malignancies, including thoracic tumors such as NSCLC and SCLC (http://meetinglibrary.asco.org/record/109650/abstract).

The median PFS and OS following initial chemotherapy in extensive stage small cell lung cancer (ES-SCLC) patients are 2 and 7 months, respectively (Ready, 2015). Maintenance therapy with pembrolizumab did not improve PFS in these patients but favorable OS suggests that some SCLC patients can benefit from maintenance pembrolizumab (Clinical trial information: NCT02359019; http://abstracts.asco.org/199/AbstView_199_183991.html). In patients with PD-L1+ SCLC who have progressed on prior platinum-based therapy, pembrolizumab is generally well tolerated and has promising antitumor activity. Enrollment in the SCLC cohort of KEYNOTE-028 is ongoing (Clinical trial information: NCT02054806). The activity of anti-PD1 agents in SCLC in the second line of therapy is reflected in ORR values of about 33 to 37% (Ott et al, 2016; Hellman et al, 2016; Antonia et al, 2016; Riess et al, 2016). In view of the above, there is good rationale to investigate the combination of galinpepimut-S plus pembrolizumab in SCLC.

1.3.1.2.4. Breast Cancer (Triple Negative; Second Line)

While many histologic/genetic variants of breast cancer have effective treatments, to date, treatments for TNBC have been minimally effective (Bianchini et al, 2016). Although WT1 expression occurs in 70 to 80% of patients with basal-type breast cancer, in specimens from TNBC (Provenzano et al, 2016; Domfeh et al, 2008), WT1 expression is approximately 8 to 15%. Nonetheless, this value may represent low sensitivity of currently used, commercially available anti-WT1 monoclonal antibodies used for IHC (Ichinohasama, 2010). Additionally, WT1 has been found to be focally amplified in a significant proportion of TNBC's and hence is still a valid immuno-oncology target, despite its low abundance observed (Craig et al,

2012). Hence, galinpepimut-S could in principle be active in a significant proportion of TNBC patients.

Current anti-PD1 therapies have shown modest monotherapy activity in recurrent TNBC (second line), as reflected in ORR values of approximately 18% (Nanda et al, 2016; Hartkopf et al, 2016; Migali et al, 2016; Emens et al, 2015; Dirix et al, 2018; Adams et al, 2016; Emens et al, 2016; Dua and Tan 2017). In view of the above, there is good rationale to investigate the combination of galinpepimut-S plus pembrolizumab in TNBC.

1.3.1.2.5. Acute Myelogenous Leukemia (AML)

AML, a clonal, neoplastic, hematopoietic disorder, is the predominant form of acute leukemia in adults. It has an incidence of approximately 2.5 per 100,000 persons and this incidence increases with age, with approximately half of patients with newly diagnosed AML older than 65 years. While most patients are able to achieve CR using anthracycline/cytarabine-based chemotherapy, the benefit associated with standard intensive chemotherapy remains debated in older patients, as well as those with medical co-morbidities because of excessive toxicity and short response duration. Response rates to conventional induction chemotherapy regimens in older patients are around 50%; and median survival is usually less than 1 year (Appelbaum et al, 2006; Döhner Het al, 2015). Despite recent advances in targeted therapy in certain subgroups of AML patients with predefined molecular aberrations (such as FLT3 internal tandem duplication [ITD], isocitric dehydrogenase 1 [IDH1] mutations, and CD33 expression; summarized in Wei and Tiong, 2017 and Stahl et al, 2017) and the advent of a liposomally delivered chemotherapy formulation as well as potential future cell-based immunotherapies (Bose P et al, 2017; Sallman and Lancet, 2017; Short and Ravandi, 2016; De Kouchkovsky and Abdul-Hay, 2016; Dombret and Gardin, 2016; Gbolahan et al, 2017), the tolerability of long term/ full-dose administration of such agents in the same subgroup of patients (those ≥ 60 years of age and/or those with comorbidities) will probably remain a challenge. The DNA methyltransferase inhibitors, azacitidine and decitabine are currently extensively used in this type of patients, because of their relatively mild side effects (Kaminskas et al, 2005). Both drugs have a complex

mechanism of action (MOA) involving epigenetic modification of entire groups of genes, thus leading to marked effects on the pattern of gene expression post- therapy (Cruijsen et al, 2014). These 2 drugs are also called hypomethylating agents (HMAs); some of their effects are pro-differentiating, while others lead to cell killing of leukemic blasts, especially those AML blasts with unfavorable cytogenetic characteristics (Maurillo, 2012).

Recent Phase 3 trials have shown the superiority of HMAs when compared with conventional care for older AML patients (not eligible for intensive treatment). HMAs are FDA-approved and widely used as frontline AML therapy for long-term disease control in patients unable to have an allogeneic (allo-) hematopoietic stem cell transplant (HSCT) or as a promising strategy to "bridge" allo-HSCT-candidate patients to the potential curative treatment of a transplant (Gbolahan et al, 2017; Ustun et al, 2013). The above notwithstanding, achievement of CR rates with HMAs in AML remains rather low, ranging from 8% to 32% depending on the series. (Gardin and Dombret 2017; Thomas and Le Jeune, 2017; Yun et al, 2008; Feldman, 2016). Another 10 to 20% of AML patients reach partial response (PR), whereas, up to 45 to 50% of patients do not respond to HMAs with either PR or CR (Sekeres, 2013). The prognosis of patients who achieve less than CR after at least 4 cycles of HMA therapy is worse than those able to achieve CR (after 4 cycles), although PR can be relatively prolonged in select cases. Of note, HMA interruption should be avoided once a sustained response, including PR, has been achieved. With regard to patients who continue on HMAs once they reach PR after the first 4 cycles, most prove unable to convert this PR into a CR (Müller and Florek, 2014; Malik and Cashen, 2014). Hence, the probabilty of such a conversion (i.e,, achievement of CR) in this subpopulation with continuation of HMAs alone after the fourth cycle is probably <5% (Cashen et al, 2010; Joeckel and Lübbert, 2012; Park et al, 2017).

WT1 is strongly and prevalently (90 to 95% of cases) expressed in AML blasts both in the peripheral blood (PB) and BM (Inoue et al, 1998; Hosen et al, 2002; Keilholz et al, 2005; Cilloni et al, 2009; Menssen et al, 1995; Inoue et al, 1997). It is also expressed in leukemic stem cells (LSCs) (Saito et al, 1997; Yong et al, 2008). WT1 expression is reliable enough to

be used as a marker of MRD in AML (as a molecular marker of relapse/response) (Alonso-Dominguez et al, 2012; Messina et al, 2014; Ogawa et al, 2003; Candoni et al, 2009; Hämäläinen et al, 2008; Mulé et al, 2016) and is typically included in MRD diagnostic multi-gene panels (Buccisano et al, 2017). As noted above, galinpepimut-S has shown activity (as assessed by median PFS and median OS since the time of initial diagnosis versus historical controls) in AML patients who were able to achieve their CR1 after standard induction chemotherapy, as well as 1 to 4 post-CR1 cycles of administration of further 'consolidation' chemotherapeutic regimen, after the completion of which they received galinpepimut-S as 'consolidation' chemotherapeutic regimen, after the completion of which they received galinpepimut-S as 'maintenance' (Maslak et al, 2007; Maslak et al, 2010; Maslak et al, 2018; SELLAS, Data on file). There is theoretical rationale for cytocidal activity by CTLs after galinpepimut-S against LSCs as well, which are especially resistant to either chemotherapy or HMAs (McCracken et al, 2016; Lane et al, 2009; Krause and Scadden, 2015). Consequently, direct WT1-specific immunization with galinpepimut-S in the context of partially controlled disease (AML achieving PR, but not CR, while on HMAs) could principally convert some of these PRs into CRs.

With regard to activity of checkpoint inhibitors in AML, to date, anti-PD1 therapies have shown modest activity in relapsed AML (second line) when given after HMAs (Lichtenegger et al, 2017; Haroun et al, 2017). However, PD1 blockers administered in combination with HMAs were shown to be associated with ORR values of up to 34% (Daver et al, 2016; Daver et al, 2017; Nagler et al, 2017; Krupka et al, 2016; Sehgal et al, 2015; http://www.targetedonc.com/publications/targeted-therapies- cancer/2017/2017-february/immune-checkpoint-approaches-in-aml-and-mds-a-next-frontier). Thus, it is very likely that a minority of patients who are unable to respond to HMA monotherapy any deeper than PR may convert their response to CR after receiving concomitant therapy with checkpoint inhibitors. The exact frequency (rate) of achievement of CR post-combination therapy in such patients remains ill defined, but is probably not exceeding 15% (approximately 50% of the ORR of 30-34% seen in studies by Daver's group at the MD Anderson Cancer Center (Daver et al, 2016; Daver et al, 2017; Boddu et al, 2018). Finally,

there is recent evidence suggesting that HMA therapy upregulates PD1 expression in the TME-infiltrated BM of AML patients as well as MHC class I molecules in blasts, thus providing cogent molecular targets for an effect of PD1 inhibition (Ørskov et al, 2015) and galinpepimut-S action, respectively. In view of the above, there is good rationale to investigate the combination of galinpepimut-S plus pembrolizumab in AML patients who cannot achieve responses deeper than PR while having been exposed to at least 4 cycles of HMAs given for first-line/upfront therapy.

2 Study Objectives

2.1 Primary Objective

Hypothesis #1: Combining galinpepimut-S with pembrolizumab could increase the clinical benefit of pembrolizumab monotherapy (Seledstov et al, 2015; Kleponis et al, 2015) as assessed by improved ORR values versus historical controls for each individual tumor type tested. This would constitute a "positive efficacy signal" (as relevant to a particular tumor type) and warrant broader future clinical investigations. Further, the combination will not increase the burden of toxicities and will have an overall similar/comparable AE profile as pembrolizumab monotherapy.

Based on the above hypothesis, the primary objectives of the study are:

- To evaluate the safety and tolerability of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers
- To evaluate the anti-tumor activity of the combination of galinpepimut-S and pembrolizumab as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 to determine if the activity seen is sufficiently promising to evaluate the combination in future clinical studies. For AML patients: to study the possibility of achieving morphologic CR (including CR with incomplete recovery of blood counts or platelets [CRi/CRp]), i.e., conversion of morphologic PR into CR/CRi/CRp. Included are the following cohorts:
    - Patients with metastatic CRC previously treated with at least 2 lines of prior systemic chemotherapy (third/fourth line population) (n = 20).
    - Patients with metastatic OvC second/third line population (n = 20)
    - Patients with advanced SCLC previously treated with 1 line of prior systemic chemotherapy (second line population) (n = 20)

- Patients with TNBC previously treated with 1 line of prior systemic chemotherapy (second line population) (n = 15)
- Patients with AML (any age) who are not eligible for allogeneic hematopoietic stem cell transplant (allo-SCT) and have only been able to achieve PR while receiving frontline therapy with HMAs (n = 15)

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the clinical benefit of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers through the analysis of time to response (TTR), time to next treatment, and duration of response (DOR).

2.3 Exploratory Objectives

Hypothesis #2: Combining galinpepimut-S with pembrolizumab could lead to the development of a robust WT1-specific immune response against patients' cancers, and potentially improve the abundance and functionality of the hosts' immunocytes within the TME (versus pembrolizumab monotherapy) (Duraiswamy et al, 2013). Positive correlative analyses (as relevant to a particular tumor type) between immune and clinical outcomes would provide a MOA framework to inform the design of future larger, randomized clinical studies in that tumor type.

Based on the above hypothesis, the exploratory objectives of this study are:

- To assess ORR per immune RECIST (iRECIST) in patients in the solid tumor arms
- To assess the frequency (rate) of achievement of MRD negativity in patients in the AML arm
- To further characterize the immunodynamics profile of galinpepimut-S and pembrolizumab combination therapy through analyses of WT1-specific CD8 and CD4 cells in PB, as well as WT1-specific memory CD8 T cells, MDSC, and T-regulatory cells [Treg] in PB
- To gauge the general immunodynamics effects upon non-antigen-specific lymphocyte immunophenotypic subtypes will be studied in PB via flow cytometry
- To assess the effects of the combination on defined biomarkers of immune checkpoint activity in the tumors (or bone marrow for AML patients) and their surrounding microenvironment (pharmacodynamics specific to pembrolizumab)
- To assess the association between selected biomarker readouts and clinical efficacy measures at specific time-points, using pre-treatment and on-treatment tumor biopsies
- To assess OS and PFS

3 Investigational Plan

3.1 Study Design

This is a Phase 1/2, open-label, non-comparative, multicenter, multi-arm study of the combination of galinpepimut-S in combination with pembrolizumab in patients with selected advanced cancers. This study will assess the efficacy and safety of galinpepimut-S and pembrolizumab and investigate the effect of galinpepimut-S and pembrolizumab on various tumor types. Patients will be followed long-term for OS and safety. The study will enroll approximately 90 patients.

Sites will primarily be major tertiary academic oncology centers and will be selected based on expertise in complicated dosing scenarios. WT1 IHC staining characteristics for all tumor/BM samples will be assessed by central pathology review (to be performed by senior pathologists who will undergo study-specific training).

3.1.1. Overall Treatment Investigational Administration Schedule

Patients will receive 70 μg sargramostim (GM-CSF) SC on Day -2 and on Day 1 before each galinpepimut-S injection. The first GM-CSF injection of each doublet will occur at the same anatomical site of the planned galinpepimut-S treatment injection within each given cycle.

The first 2 galinpepimut-S injections will initially be administered as monotherapy every 3 weeks (Week 0 and Week 3). Thereafter, galinpepimut-S will be co-administered with pembrolizumab every 3 weeks for 4 additional administrations (for the galinpepimut-S initial immunization induction phase series; weeks 6-15) to coincide with the per label pembrolizumab dosing frequency. After that, there will be one un-paired administration of pembrolizumab (week 18), and then galinpepimut-S will be resumed on an every 3-week schedule for 6 additional doses (early immune booster phase; weeks 21-36). At the end of this phase, there will be a 12-week interval where 3 unpaired administrations of

pembrolizumab will occur (weeks 39-45), and then galinpepimut-S will be resumed on an every 12-week schedule for 4 additional doses (late immune booster phase; weeks 48-84). After 84 weeks, continuing non-progressed patients will be treated with pembrolizumab alone up until week 111. Galinpepimut-S will be administered 30-60 minutes after the completion of IV infusion of pembrolizumab on Day 1 of each cycle during which the 2 drugs are being co-administered.

Pembrolizumab will be administered at a dose of 200 mg intravenously every 3 weeks on Day 1 of each cycle (3-week cycles) starting on Study Week 6 and continuing for up to 2 years thereafter (Study Week 111). To monitor for any adverse reactions, specifically for systemic anaphylaxis type reactions against either GM-CSF or galinpepimut-S, patients will remain in the clinic for approximately 30 minutes following each GM-CSF or galinpepimut-S injection. Safety assessments will be conducted at every visit. The end of treatment (EOT) visit will occur 30 days after the last injection.

Specifically for patients in the AML arm, the timing of the administration of the investigational therapies (pembrolizumab and galinpepimut-S) with respect to administration of hypomethylating agents (HMAs) will be as follows:

- AML patients on cycles #1 – 4 of HMA on-label therapy (treated according to standard clinical care) will be pre-screened to gauge potentially eligibility for the study.
- If restaging bone marrow biopsy immediately after the completion of cycle #4 of HMA therapy demonstrates morphological partial response (PR), then such patients become eligible for the study and can initiate investigational therapy (pembrolizumab and galinpepimut-S), as long as the latter commences prior to the initiation of cycle #5 of the HMA.
- Reasonable efforts will be made by the Contracted Research Organization (CRO), Cancer Insight, LLC, at actively enrolling clinical sites to initiate investigational therapy within 14 +/7 days from the completion of cycle #4 of HMA therapy, to ensure relative homogeneity in the initiation timing relationship between the two

therapeutic modalities, i.e., HMA and investigational therapy.
Furthermore, for clarification purposes, each cycle of therapy in patients in the AML arm will be defined by the frequency of administration of the study investigational agents (pembrolizumab and galinpepimut- S), i.e., 3 weeks. This clarification is important, because:

a. patients in the AML arm will continue their HMA therapy throughout the administration of study investigational agents and

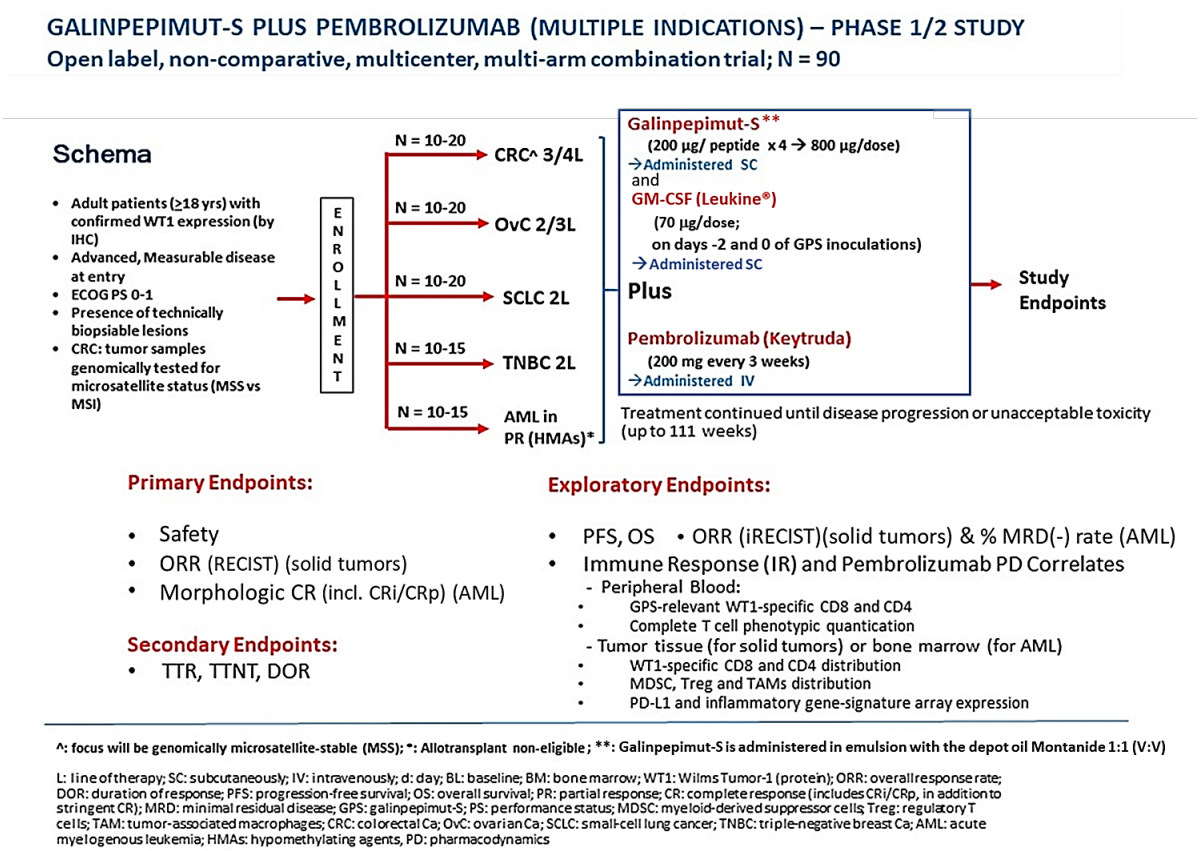
b. the timing of initiation between HMA cycle #5 and that of the first administration of investigational therapies are de-linked.

The study design is shown in

Figure 12 and the overall treatment schedule is provided in Figure 13.

The study endpoints are defined in Section 7.

Figure 12 Study Design



3.1.2. Rationale of Study Design

There is clearly an unmet need for novel and effective therapy to improve responses and prolong disease remission/progression-free intervals already achieved with checkpoint blockade monotherapy (Farkona et al, 2016). The objectives of this proposed clinical study

are: (i). to explore clinical outcomes (safety and potentially promising activity) in tumors using a combination of agents that improve immune-mediated anticancer effects, namely, pembrolizumab and galinpepimut-S, and (ii). to maximize the chances of detecting a clinically meaningful efficacy signal in comparison to historical monotherapy data (with pembrolizumab alone) for further validation in larger, randomized trials.

To meet these objectives, the current design of a Phase 1/2 open-label, non-comparative, multicenter, multi-arm clinical study was chosen, as it has been used successfully in similar studies beforehand (Menis et al, 2014; Toulmonde et al, 2018; Goldberg et al, 2016), and therefore considered as highly suitable for this trial.

4.0. Patient Selection and Withdrawal Criteria

4.1. Selection of Study Population

Patients will be enrolled into the study only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Patients who do not initially meet all of the inclusion criteria and none of the exclusion criteria may be allowed to retest for laboratory evaluations and other procedures within 28 days of signing the informed consent form (ICF) without being considered a rescreen. If the patient then meets all inclusion/exclusion criteria, they are permitted to be enrolled into the study. If a patient does not meet inclusion/exclusion criteria within the 28 days of signing the ICF, the patient will be considered a screen failure and may be allowed to re-screen with a newly signed ICF up to 2 times.

4.1.1. Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

Type of Participant and Disease Characteristics

1. Is willing and able to understand and provide signed informed consent for the study that fulfills Institutional Review Board (IRB) guidelines
2. Male or female patients ≥ 18 years of age on the day of signing informed consent.
3. Has histologically or cytologically-confirmed advanced or metastatic solid tumors who have disease progression after treatment with available therapies for metastatic disease that are known to confer clinical benefit, or are intolerant to treatment, or refuse standard treatment in the context of the particular line of treatment defined in

this protocol (refer to #5 below) or, specifically for AML, demonstrate as their best observed response after 4 cycles of HMA therapy the status of "partial response" per European LeukemiaNet (ELN) criteria and meet the additional specified requirements for the cohort of the study they will enroll into.

4. All patients will be tested for WT1 expression via IHC in both their initial primary tumor and recent biopsy of metastatic disease at the time of screening for study entry, or, specifically for AML, leukemic blasts either in the BM or PB. Specifically:
    a. Testing of patient's archived (paraffin embedded, unstained slides) as well as freshly biopsied tumor nodules prior to study entry must be positive for WT1 protein expression.
    b. WT1 expression: The IHC technique to be used for the detection of WT1 in tumor tissue (or AML blasts within the bone marrow - applicable only for subjects in the AML arm) is described in detail by Dupont et al. (Dupont et al, 2004) using the anti-WT1 monoclonal antibody H-1/ sc-393498 (Santa Cruz Biotechnology, Dallas, TX, USA). In more detail, formalin-fixed, paraffin- embedded tissue sections are subjected to immunohistochemical testing using the streptavidin-biotin method. WT1 is used at a dilution of 1:4,000. A heat-induced epitope retrieval system is used for the antibody, involving steam-heat incubation with citrate at pH 6 for 30 min at 97^{o}C. Human Wilms tumor or malignant pleural mesothelioma samples will used as a positive control for WT1, with appropriate negative controls. Positive WT1 nuclear staining is defined as the presence of any nuclear staining in >5% of tumor cells and positive WT1 cytoplasmic staining was defined as the presence of any cytoplasmic staining in >5% of tumor cells. WT1 expression is graded according to an adaptation of the German Immunoreactive Score (IRS) (Remmele and Stegner, 1986 & 1987). Briefly, the IRS assigns subscores for intensity of immunoreactivity (0–3) and distribution of immunoreactivity (0–4; based on percent positive cells within a cluster), which when multiplied, yield a product (IRS score, ranging from 0 to 12) that allows categorization of

weak, moderate, and strong immunoreactivity. For WT1, negative or weak immunoreactivity (scores 0–3) are considered negative, while moderate or strong immunoreactivity (scores 4–12) are considered positive.
Assessment of all tumor/BM biopsies for WT1 expression using the German IRS assignment system will be performed centrally by an experienced Pathologist using a standardized form, which also depicts the IRS scale for ease of reference. This form is shows as Appendix 12.3 of this protocol.
Due to essential non-expression of WT1 in normal tissues, the specificity for WT1 expression in tumors under study is essentially 100%. The sensitivity of the IHC assay is defined in relevant sections of the protocol for each tumor type under study, ranging from 40% in SCLC to >90% in AML cases. All above specimens will undergo central pathology review.

5. Patients may have received a specific maximum allowable number of prior lines of therapy for metastatic/advanced disease, as follows:
    a. CRC: 2 or 3 lines; b. OvC: 1 or 2 lines; c. SCLC: 1 line; d. TNBC: 1 line; and e. AML: 0 lines (allo-SCT-eligible status or patients with relapsed [2nd line] AML not allowed)
6. Patients should have experienced resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
7. Specifically for patients in the AML arm, the following subject subgroups are eligible:
    a. Frontline (1st line) patients treated with HMAs since their initial AML diagnosis
    b. Patients who have required cytoreductive therapy with hydroxyurea or leukapheresis at the time of their initial AML diagnosis, and who subsequently seamlessly transitioned to HMA therapy

c. Subjects who have experienced induction early failure after initial therapy with 1 - 2 cycles of a standard chemotherapy ("7+3" and similar regimens) and subsequently immediately treated with HMAs

as long as such patients have achieved PR as their best observable response after 4 cycles of HMA therapy (per European LeukemiaNet [ELN] criteria).

8. AML patients should continue treatment with HMAs as long as they cannot achieve a response deeper than PR after the completion of administration of 4 cycles of HMAs.
9. If female, patient is eligible to participate if she is not pregnant, not breast-feeding, and at least 1 of the following conditions:
   a. Not a woman of childbearing potential (WOCBP)
   b. A WOCBP who agrees to follow contraceptive guidance (agree to use an adequate method of contraception) starting 30 days prior to the administration of the first dose of study therapy and continuing through 4 months after the last study treatment. The effect of galinpepimut-S on the fetus is unknown.
10. Male patients of childbearing potential must agree to use an adequate method of contraception, starting with the first dose of study therapy through 4 months following the last study treatment. It is unknown whether galinpepimut-S affects the sperm, or could be transmitted to the patient's partner during sexual activity.

Informed Consent

11. Patients (or legally acceptable representative if applicable) should provide written informed consent for the trial.
12. Patients should have measurable/demonstrable active malignant disease per below:
    a. For patients with solid tumors: Have measurable disease based on RECIST 1.1 as determined by the as assessed by the local site

investigator/radiology. Measurable disease is defined as at least one lesion that can be accurately measured in at least two dimensions with spiral CT scan. Minimum measurement must be > 15 mm in the longest diameter by > 10 mm in the short axis. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

b. For AML patients: Have evidence of morphologic partial response (decrease of BM blast percentage to 5% to 25% and decrease of pretreatment BM blast percentage by > 50%) but absence of extramedullary disease, as defined initially by the AML Working Group Criteria (Cheson et al, 2003) and also quoted in the more recent ELN criteria (Döhner et al, 2010). Leukemic blast burden will be determined by a local site investigator (physician) upon clinical and BM morphologic assessment. AML patients should also have received/completed 4 cycles of HMA therapy and have PR as their best observed response at the end of these 4 cycles.

13. Patients should have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
    Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).
14. Patients should have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix).
15. Have adequate organ function as defined in Table 1. Specimens must be collected within 10 days prior to the start of study treatment.

Table 1 Definition of Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN

Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [2] Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

16. Patients should be willing and able to return to the clinical site for adequate follow-up, as required by this protocol.

Additional Inclusion Criteria for Selected Tumor Types:

(i). CRC (third/fourth line)

a. Histologically or cytologically documented adenocarcinoma of colon or rectum at the time of initial presentation.
b. Metastatic CRC with documented disease progression (per standard criteria) after the last administration of standard therapies or intolerance to standard therapies (and approved

therapies must have included all the following a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and, if KRAS wild-type, cetuximab or panitumumab). Prior use of (and failure after) regorafenib or trifluridine/tipiracil is allowed, but not mandated.

(ii). OvC (second/third line)

a. Histologically diagnosed ovarian, fallopian tube or primary peritoneal cancer at the time of initial presentation.
b. Patients will have either relapsed or be disease resistant to their prior therapy. Interval surgery is permitted, but patients must have objective evidence of disease on computed tomography (CT) or magnetic resonance imaging (MRI), with concomitant CA-125 increase and/or biopsy showing OvC (only for recurrent disease).
c. Patients should have received platinum-containing chemotherapy and been designated as harboring platinum-refractory or -resistant disease. Additionally, all eligible subjects should have either received (or been offered) bevacizumab therapy, and those with BRCA germline mutations (gBRCA mut) should have been offered therapy with poly-ADP ribose polymerase (PARP) inhibitors (olaparib, rucaparib or niraparib).

(iii). SCLC (second line)

a. Histologically or cytologically confirmed SCLC based on biopsy of the tumor at initial presentation.
b. Asymptomatic or treated brain metastases are allowed.
c. Patients must have measurable disease (by CT or MRI) after they progressed or were resistant to 1 prior systemic therapy.

(iv). TNBC (second line)

a. Histologically proven metastatic breast carcinoma with triple negative receptor status (estrogen receptor, progesterone receptor, and human epidermal growth factor

receptor 2 [HER2] negative by IHC and fluorescence in situ hybridization [FISH], per standard criteria). Patients who are weakly positive for the estrogen or progesterone receptor (i.e., ≤ 5%) are eligible.

b. Patients must have measurable disease (by CT or MRI) after they progressed or were resistant to 1 prior systemic therapy.
c. Patients have undergone second line therapy after residual or recurrent disease after first line therapy. First line therapy may include:
    a. Neoadjuvant therapy if macroscopic disease is still present after surgery OR
    b. Adjuvant therapy but only if the macroscopic relapse occurs > 6 months from the start of study treatment with pembrolizumab.

(v). AML

a. Pathologically or morphologically confirmed de novo or secondary AML at the time of initial diagnosis.
b. Achievement of no better than morphologic PR, as defined initially by the AML Working Group criteria (Cheson et al, 2003), and also quoted in the more recent ELN criteria (Döhner et al, 2010), while on active treatment with HMAs and at the time of completion of the 4th HMA treatment cycle.
c. AML patients are eligible only if they received first line therapy with HMAs (decitabine or azacitidine) for 4 cycles and achieved only PR at the end of cycle 4.
d. AML patients shall remain on HMA therapy while receiving investigational therapies.

4.1.2. Exclusion Criteria

Any prospective patient will be excluded from the study if any of the following criteria apply:

Medical Conditions

Pregnancy Exclusion:

1. A WOCBP who has a positive urine pregnancy test (e.g. within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

2. Has disease that is suitable for local therapy administered with curative intent.3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE

4. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to treatment.

Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

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

5. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

6. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

8. Has undergone prior allogeneic hematopoietic stem cell transplantation

Diagnostic assessments

9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Steroids taken as short-term therapy (≤ 7 days) for antiemesis are permissible.

10. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years, even if currently inactive or unapparent.

Note: Specifically, AML patients with prior history of myelodysplastic syndromes or myeloproliferative neoplasms are not excluded. Participants in any of the study arms (solid tumors or AML) with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy, as well as patients with prostate cancer managed clinically with “watchful waiting” are not excluded.

11. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

13. Has known hypersensitivity to Montanide or vaccine adjuvants.

14. Had a previous clinically significant systemic allergic reaction to Montanide, sargramostim (GM-CSF), or filgrastim (G-CSF).

15. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

16. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

17 Has an active infection requiring systemic therapy.

18. Participants with known human immunodeficiency virus (HIV) and/or history of Hepatitis B or C infections, or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA are excluded. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

19. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator. This includes any serious, intercurrent, chronic, or acute illness, such as cardiac disease (New York Heart Association [NYHA] class III or IV), hepatic disease, or other illness considered by the investigator as an unwarranted high risk for investigational drug

treatment.20. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

21. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 30 days after the last dose of study treatment.

22. Has had an allogeneic tissue/solid organ transplant.

23. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (**excluding GM-CSF**, but including G CSF or recombinant erythropoietin) within 4 weeks prior to first study treatment.

4.1.2.1. Additional Exclusion Criteria for Selected Tumor Types

(i). CRC: None

(ii). OvC: None

(iii). SCLC: Mixed histology SCLC malignancies

(iv). TNBC: None

(v). AML:

a. Planned/anticipated HSCT (autologous or allogeneic, with any degree of match donor); acute promyelocytic leukemia (APL; M3 or any morphologic and molecular variants, inclusive); history or current diagnosis of CNS leukemia

b. Relapsed (Second line) patients; Note: Patients who received any chemotherapy ("3 + 7" or similar chemotherapy regiman) for 1- 2 cycles during initial induction therapy

in the first-line setting and subsequently immediately switched to HMAs are not excluded.

4.2. Withdrawal of Patients from the Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through the end-of-treatment visit, which can be up to a maximum of 111 weeks after enrollment, or a total of 115 weeks inclusive of screening. All patients will then be followed for primary, secondary, and exploratory endpoints (including PFS and OS), unless they die or formally withdraw their consent for survival follow-up.

Withdrawal of consent must be patient initiated. This applies either if the patient is declaring that they no longer wish to receive study treatment or attend on-treatment study visits or that they will not allow study investigators to make any further efforts to follow them off-treatment for study outcomes.

4.2.1. Reasons for Withdrawal/Discontinuation

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

Patients may voluntarily withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. The investigator may withdraw a patient if it is in the best interest of the patient. The Sponsor also reserves the right to discontinue the study at any time for either clinical, administrative, or business reasons, and to discontinue participation by an individual investigator or site for poor enrollment or noncompliance.

Patients may be removed from study treatment, from on-treatment study assessments, or from off-treatment study assessments but continue to be monitored in the study for the following reasons:

- Recurrent Grade 2 pneumonitis

- Patient was erroneously admitted into the study or does not meet entry criteria
- Patient experiences a serious or intolerable AE or clinically significant laboratory abnormality that, in the opinion of the investigator, would affect the ability of the patient to continue on the clinical study
- Patient has progressive disease
- Patient voluntarily decides to withdraw
- Patient is lost to follow-up
- Patient requires treatment with any prohibited medication outlined in the exclusion criteria and/or Section 5.6 other than the use of appropriate medications for the treatment of AEs under the direction of the investigator
- Patient is noncompliant with the study procedures and scheduled assessments
- Patient develops an intercurrent disease or medical condition that, in the opinion of the investigator, would affect the ability of the patient to continue on the clinical study.

Discontinuation of treatment may be considered for patients who have attained a confirmed CR (either solid tumors or AML, using the corresponding response definitions), as follows: Such patients would have attained CR after having been treated for **at least** 10 cycles of galinpepimut-S, i.e., at least 30 weeks:2 cycles of galinpepimut-S monotherapy (6 weeks) followed by 9 cycles of pembrolizumab (an additional 24 weeks). Such patients in CR should also receive 2-additional cycles of the combination (2 doses of pembrolizumab and galinpepimut-S [until Week 36]) beyond the date when the initial CR was declared, so that at least 12 of the total 16 (75%) planned doses of galinpepimut-S would have been administered. At that time, 12 out of a planned total of 36 treatments (2 years) with

pembrolizumab (corresponding to approximately 33% of the total planned pembrolizumab treatments).

4.2.2. Handling of Withdrawals

If a patient discontinues study treatment but remains on study, every effort should be made to continue the patient's assessments according to the schedule of assessments (Section) through the end of the study. For patients who withdraw from the study, procedures and assessments for the end-of-treatment (EOT) visit (Section 6.1.3) should be performed at the time of discontinuation of treatment or as soon as possible thereafter (unless the patient withdraws consent to do so). A follow-up assessment performing end of treatment (EOT) procedures should be undertaken 4 weeks after discontinuation of study treatment.

If a patient fails to return for scheduled visits, a documented effort must be made to determine the reason. If the patient cannot be reached by telephone, a certified letter should be sent to the patient (or the patient's legally authorized representative, if appropriate) requesting contact with the investigator. This information should be documented in the study records.

Before enrollment into the study, the investigator or designee must explain to each patient that for evaluation of study results, the patient's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and IRB/independent ethics committee (IEC). It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each patient, or if appropriate, the patient's legally authorized representative. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the patient, and the patient will be removed from the study.

Upon occurrence of a serious or intolerable AEs, the investigator will confer with the Sponsor. It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor, and will be clearly documented on the appropriate electronic case report form (eCRF).

4.2.3. Replacements

There will be no replacements in this study.

5. Study Treatments

5.1. Method of Assigning Patients to Treatment

Once the investigator confirms that the patient has met all eligibility criteria, the patient will be enrolled in the study by the local investigators and their teams. Trial treatment should begin on the day of enrollment or as close as possible to the date on which the patient is enrolled. The investigator is responsible to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments is in accordance with the protocol and any applicable laws and regulations.

5.2. Treatments Administered

Refer to Table 8 (Schedule of Assessments) for additional details.

5.2.1. Galinpepimut-S

Each of the 4 peptides will be supplied at a concentration of 0.2 mg/vial. After reconstitution with 0.6 mL sterile water for injection (SWFI), each peptide will be at a concentration of 0.4 mg/mL (400 µg/mL of each peptide) combined in a single sterile solution in a buffer consisting of 10 mM histidine, pH 6.0 + 0.05% ethylene diamine tetra acetic acid (EDTA). As galinpepimut-S will comprise 50% (0.5 mL) of the study treatment injection administered, the actual dose of each peptide is 200 µg (with the total 4 active peptides equaling 800 µg). On galinpepimut-S administration days, blood samples will be collected before study treatment administration. Before injection, study staff will assess the immunization site. Patients will receive an injection of GM-CSF (refer to Section 5.2.3).

A 1-mL dose of galinpepimut-S will be administered subcutaneously (SC) on the arm, leg, or torso of the patient, and should be positioned at least 5 cm away from the previous site of the study treatment injection.

A maximum of 16 total injections will be administered as follows:

- First 2 galinpepimut-S injections: every 3 weeks (×2). Thereafter, galinpepimut-S will also be administered every 3 weeks to coincide with pembrolizumab treatment as detailed below:
- Injections 3 to 6: every 3 weeks (between Weeks #6 and #15). The first series of 6 injections of galinpepimut-S (I + II) define the initial immunization induction phase.
- Injections 7 to 12: every 3 weeks (between Weeks #21 and #36). The second series of injections of galinpepimut-S define the early immune booster phase.
- Injections 13 to 18: every 12 weeks (between Weeks #48 and #84). The series of the last 4 injections of galinpepimut-S define the late immune booster phase.
- As galinpepimut-S will be co-administered with Montanide, specific information about this emulsifying agent is provided in the Montanide Investigator Brochure.

Every effort should be made to follow the administration schedule for galinpepimut-S and pembrolizumab. If a patient misses a scheduled administration of either the combination or pembrolizumab alone, the drug(s), should be administered as soon as possible. If the patient is more than one-half the time interval to the next scheduled administration, the patient should skip that preplanned administration and have the next administration on schedule.

Galinpepimut-S will be administered 30-60 minutes after the completion of IV infusion of pembrolizumab on Day 1 of each cycle during which the 2 drugs are being co-administered.

Refer to Section 5.2.2 for Montanide ISA 51 VG administration.

5.2.2. Montanide ISA 51 VG

Galinpepimut-S treatment preparation will require reconstitution of the lyophilized powder with SWFI, followed by a mixture of the peptide solution of galinpepimut-S with the

immunologic adjuvant Montanide ISA 51 VG as an emulsion to a total volume of 1 mL. The study treatment solution will comprise 50% (0.5 mL) of galinpepimut-S and 50% (0.5 mL) Montanide.

Galinpepimut-S includes concomitant administration of Montanide (adjuvant) on Day 1 of all sessions of administration of this direct immunizer.

Galinpepimut-S will be subsequently mixed in a water-in-oil emulsion with the oily adjuvant Montanide ISA 51 at a 1:1 ratio. The resulting final emulsion will be administered to the patient SC as a 1 mL injection.

5.2.3. Sargramostim (GM-CSF)

Patients will receive 70 µg sargramostim (GM-CSF) SC on Day -2 and on Day 1 before each galinpepimut-S injection. Patients will remain in the clinic for approximately 30 minutes following receipt of GM-CSF. This injection will occur at the same anatomical site of the next planned study treatment injection.

5.2.4. Pembrolizumab

Treatment for pembrolizumab is outlined below in Table 2.

Table 2 Treatment with Pembrolizumab (irrespective of whether it is administered alone or concomitantly with galinpepimut-S)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) and begins at Week 6	Experimental

Pembrolizumab will be administered as a dose of 200 mg using 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 between -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 and administration of infusion solution.

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

Discontinuation of treatment may be considered for patients who have attained a confirmed CR (either solid tumors or AML, using the corresponding response definitions), as follows: Such patients would have attained CR after having been treated for **at least** 10 cycles of galinpepimut-S, i.e., at least 30 weeks: 2 cycles of galinpepimut-S monotherapy (6 weeks) followed by 9 cycles of pembrolizumab (an additional 24 weeks). Such patients in CR should also receive 2-additional cycles of the combination (2 doses of pembrolizumab and galinpepimut-S [until Week 36]) beyond the date when the initial CR was declared, so that at least 12 of the total 16 (75%) planned doses of galinpepimut-S would have been administered. At that time, 12 out of a planned total of 36 treatments (2 years) with pembrolizumab (corresponding to approximately 33% of the total planned pembrolizumab treatments).

Note: The number of treatment administrations is calculated starting with the first dose of galinpepimut-S.

5.3. Identity of Investigational Drug Product

Table 3 provides a description for each of the investigational products.

Table 3 Description of Investigational Products

Product	Supplied as:
Galinpepimut-S	0.8 mg sterile, white preservative-free powder filled into a 2-mL colorless glass vial provided by the sponsor. Lyophilized galinpepimut-S requires reconstitution with sterile water (not provided by the sponsor)
Montanide ISA 51 VG	3-mL amber glass vial provided by the sponsor
Sargramostim (GM-CSF)	250-µg sterile, white, preservative-free powder in a single-use vial provided by the sponsor. Lyophilized sargramostim requires reconstitution with sterile water (not provided by the sponsor)
Pembrolizumab	Solution for infusion is supplied by the sponsor as 100 mg/vial liquid DP (manufactured using the fully formulated DS with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier) in a single use glass vial (will be provided by Merck).

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; USP, United States Pharmacopeia.

5.3.1. Galinpepimut-S

Galinpepimut-S is a lyophilized preparation of 4 different WT1-derived synthetic analog peptides considered as a multicomponent single drug product. Each of the 4 peptides will be supplied at a concentration of 0.2 mg/vial. After reconstitution with 0.6 mL SWFI, each peptide will be at a concentration of 0.4 mg/mL (400 µg/mL of each peptide) combined in a single sterile solution (after reconstitution into liquid/soluble form) in a buffer consisting of

10 mM histidine, pH 6.0 + 0.05% EDTA. As galinpepimut-S Drug Product will comprise 50% (0.5 mL) of the study treatment injection administered, with the other 50% of the total injectate volume being Montanide, the actual dose of each peptide is 200 µg per inoculation (with the total 4 active peptides equaling in weight 800 µg per inoculation). The peptides include 1 WT1-derived peptide (A1) to stimulate CD8+ responses, 2 WT1 long peptides (WT1-427 L, WT1-331 L) to stimulate CD4+ responses, and 1 modified peptide (WT1-122A1 L) that is able to stimulate both CD4+ and CD8+ cells. The WT1-A1 and WT1-122A1 L contain a mutated aminoacid (aa) residue (R126Y), and are, therefore, heteroclitic. The sequence for the heteroclitic WT1-A1 peptide is embedded within the sequence of the longer WT1-122A1 L peptide. The structural formulas (aa sequences) of the vaccine administered are depicted in Table 4.

Table 4 Structural Formula of Galinpepimut-S

Peptide Sequences (position)	Peptide Length	Computationally Predicted Binding to HLA
WT1-A1: *YMFPNAPYL (126–134)	9 aa	A0201, A0301, A2402, B1501, B3901
427 long: RSDELVRHHNMHQRNMTKL (427–445)	19 aa	B0702, B08, B2705, B4001, B5801, and numerous HLA-DRB1-XX
331 long: PGCNKRYFKLSHLQMHSRKHTG (331–352)	22 aa	
122A1 long: SGQA*YMFPNAPYLPSCLES (122–140)	19 aa	A0201, A0301, A2402, B1501, B3901, B0702, B08, B2705, B4001, B5801, and numerous HLA-DRB1-XX

Abbreviations: DR, D-related; HLA, human leukocyte antigen; WT1, Wilms' tumor 1 antigen.

Peptide abbreviations: A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; Y, tyrosine. *Designates single amino acid substitution (R>Y) by deliberately designed mutations in the heteroclitic peptides

The Drug Substance for the 4 peptides are manufactured at Polypeptide Laboratories, Inc. (Torrance, CA, USA). The lyophilization process, manufacturing of Drug Product (API) and sterile fill and finish under Good Manufacturing Practice conditions are performed by Corden Pharma S.p.A. (Caponago, Italy). Each lot of the lyophilized peptide powder are tested for physicochemical stability, sterility, and API content at PPD GMP Laboratories, Inc. (Middleton, WI, USA).

Galinpepimut-S is considered as a multicomponent single drug product comprised of 4 peptides (described above) in a sterile lyophilized powder containing 0.8 mg peptides. Galinpepimut-S will be provided as a sterile, white, preservative-free powder filled into a 2 mL vial, for reconstitution with 0.6 mL SWFI. After reconstitution with SWFI, the peptides will be in a buffer of 10 mM histidine, pH 6.0 + 0.05% EDTA. Galinpepimut-S will be mixed in a water in oil emulsion with the oily adjuvant Montanide at a 1:1 ratio. The resulting final emulsion, which is administered as study treatment, will also be referred to as galinpepimut-S for practical product administration purposes in this protocol.

The total amount of the finished product is 0.96 mg (overfill of 20%) filled into a 2-mL colorless glass vial. The vial should be stored at the site at or below −20°C until use.

5.3.2. Montanide ISA 51 VG

Montanide ISA 51 VG is an adjuvant (NSC # 737063) produced by SEPPIC, Inc. (Fairfield, NJ) under Good Manufacturing Practice and is composed of a light oil and a surfactant system designed to make a water-in-oil emulsion. Montanide ISA 51 VG has been clinically tested based on a vegetable grade formulation used to emulsify the peptides. Montanide ISA 51 VG has proved to be a very efficient adjuvant, activating the cellular and the humoral

immune response. Montanide ISA 51 VG has been administered to more than 10,000 patients throughout the world. Montanide is packaged in 3-mL amber glass vials. The adjuvant is stored between 15°C to 30°C and must not be frozen.

5.3.3. Sargramostim (GM-CSF)

Sargramostim (GM-CSF) is manufactured by Partner Therapeutics, Inc. (Lexington, MA) , under Good Manufacturing Practices and is provided in lyophilized form as a 250-µg sterile, white, preservative-free powder that requires reconstitution with SWFI. GM-CSF must be stored at 2°C to 8°C. For this study, the vial of GM-CSF is intended for single-use only.

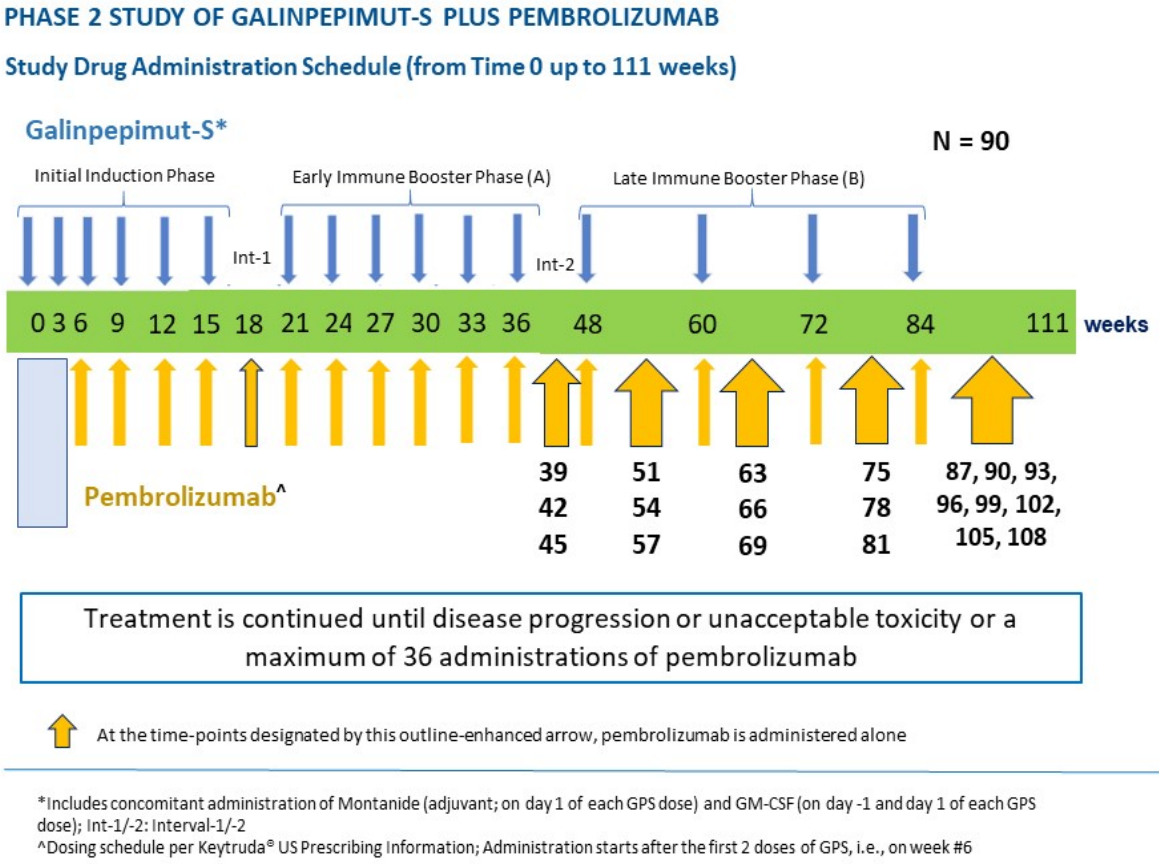
5.3.4. Pembrolizumab

The pembrolizumab treatment to be used in this trial is outlined in Table 2 in Section 5.2.4. above.

5.3.5. Overall Treatment Schedule

The overall treatment administration schedule is shown in Figure 13 below:

Figure 13 Overall Treatment Administration Schedule



5.3.6. Toxicities

Galinpepimut-S: The potential toxicities/side effects of galinpepimut-S include:

Likely:

- Induration at injection site

Less likely:

- Arthralgias, myalgias
- Fever
- Headache
- Edema
- Allergic reaction

Rare:

- Elevated liver function tests
- Elevated kidney function tests
- Shortness of breath

Montanide ISA 51 VG: The potential toxicities/side effects of Montanide ISA 51 VG include:

- Mild inflammation at injection sites
- Occasional fever
- Allergic reactions have been observed rarely

Sargramostim (GM-CSF): Sargramostim is an approved product, available in the US since 1991. It has been used in a number of studies as an immunologic adjuvant with the presumed benefit mediated through effects on dendritic and other antigen-presenting cells. Several human vaccine studies in melanoma and other human malignancies have reported both

encouraging immunologic and clinical results. More recently, 2 melanoma vaccine studies have reported a harmful effect of GM-CSF when used as a vaccine adjuvant (Faries et al, 2009; Slingluff et al, 2009). While it is important to recognize a potential negative effect, this study uses a different vaccine with a different dose of GM-CSF in a different disease.

The potential toxicities/side effects of GM-CSF include (at standard doses of 250 µg/m^2/day for 5 to 14 days):

- Edema
- Fluid retention
- Headache
- Myalgia
- Arthralgia
- Dyspnea
- Allergic reactions
- Patients with pre-existing renal and/or hepatic disorders may demonstrate elevations in serum creatinine or bilirubin/transaminases, respectively.

Pembrolizumab toxicities are detailed in Section 5.3.6.3.1.

5.3.6.1. Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0, (published in November 2017), as per the following link:.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

For patients enrolled across all active solid tumor cohorts (colorectal, ovarian, small cell lung cancer, breast cancer), the dose-limiting toxicity (DLT) window of observation will be at least one (1) cycle following the co-administration of galinpepimut-S in combination with pembrolizumab. A DLT is judged by the investigator to be possibly, probably, or definitely related to study drug administration. AML-specific DLTs will be considered separately (Section 5.3.6.2).
The occurrence of any of the following toxicities will be considered a DLT (except for AML; please see Section 5.3.6.2), if judged by the investigator to be possibly, probably, or definitely related to study drug administration:

1. Grade 4 nonhematologic toxicity (not laboratory)
2. Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with bleeding
3. Any nonhematologic AE ≥ Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Grade 3 nonhematologic toxicity (not laboratory) lasting > 3 days despite optimal supportive care.
5. Any Grade 3 or Grade 4 nonhematologic laboratory value if:

- Clinically significant medical intervention is required to treat the patient, or
- The abnormality leads to hospitalization, or
- The abnormality persists for > 1 week.
- The abnormality results in a drug-induced liver injury (DILI)
- Exceptions: clinically nonsignificant, treatable, or reversible laboratory abnormalities, including liver tests, uric acid, etc.

6. Febrile neutropenia (FN) Grade 3 or Grade 4:
    - Grade 3 is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour
    - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
7. Any treatment-related toxicity that causes the patient to discontinue treatment during the period from the first administration of galinpepimut-S until the completion of the first cycle of galinpepimut-S plus pembrolizumab combination therapy.
8. Missing > 25% of pembrolizumab doses as a result of drug-related AE(s) during the first cycle of combination therapy.
9. Thrombocytopenia < 25,000/mm^3 if associated with:
    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit (ICU)

10. Prolonged delay (> 2 weeks) in initiating Cycle 2 of combination therapy due to treatment-related toxicity
11. Grade 5 toxicity.

Missing > 25% of the doses of either investigational agent as a result of drug-related AE(s) during the period from first administration of galinpepimut-S and up until the completion of

the first cycle of the co-administration of galinpepimut-S in combination with pembrolizumab.

Staggered Early Enrollment:

To minimize exposing subjects to the risk of potential unknown acute and subacute toxicities of combining pembrolizumab with galinpepimut-S, the inter-dosing interval in-between the first consecutive three (3) subjects to be enrolled in this study arm will be one (1) week following the administration of the first dose of pembrolizumab in these patients.

DLT assessment and actions will be as follows (unless stopping rules apply):

- If 2 or fewer patients of these first 6 patients have DLTs, enrollment can continue for up to another 6 patients across these arms with no dose adjustments made. If DLTs are observed in more than 2 patients of the first 6, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the immediately subsequent administration after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.
- In the next 6 patients (patients 7 to 12), if again, 2 or fewer of these patients have DLTs observed, enrollment can continue. If DLTs are observed in more than 2 of patients 7 to 12, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled, , but pembrolizumab will continue as scheduled.
- If DLTs are observed in more than 2 patients of the first 6 (patients 1 to 6) and again in more than 2 patients of the next 6 (patients 7 to 12), the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the 2 immediately subsequent administrations after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.

- If DLTs continue to be observed above 2 per every 6 patients beyond these first 12 patients, and even after the changes in administration of galinpepimut-S, the study will be stopped and the safety data will be examined by the sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study.

- Should a given patient experience any of the above DLTs at any time after the completion of the first cycle of co-administration of galinpepimut-S in combination with pembrolizumab, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled, but pembrolizumab will continue as scheduled.
- If another DLT occurs in that next cycle, the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT, but pembrolizumab will continue as scheduled.
- If no DLTs re-occur after the above periods of doubly 'spaced out' administrations, then the patient should revert back to the initial GPS Q3W schedule (as per the initial dosing frequency/ investigational agent administration schedule).
- If a DLT occurs after these dose modifications in subsequent cycles, the patient will be discontinued from the study.

The above dose density modifications in response to DLTs is further summarized in the bulleted list of actions below:

- First DLT → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **once thereafter**, i.e. **for 1 additional cycle** → DLT resolution → Return to per protocol schedule of GPS administration
- Second DLT (after reverting to the per protocol schedule) → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **twice thereafter**, i.e. **for 2 additional cycles** → DLT resolution → Return to per protocol schedule of GPS administration

- Third DLT (occurring either after reverting to the per protocol schedule or during the 'spread out' schedule to manage the 2nd DLT above) → Discontinue patient from study.
- N.B.: In all above modifications of the dose density of galinpepimut-S, as all intervals (in weeks) between 2 successive GPS administrations are multiples of three (3) by design, following these rules, co-administration with pembrolizumab is always secured.

Stopping Rules:

- Development of any SAEs at least "possibly attributable" to the study agent(s) in 2 out of the first 6 patients in the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.
- The fraction of patients experiencing an SAE at least "possibly attributable" to the study agent(s) exceeds 1/3, at any time during study implementation beyond the first 6 patients.
- Death at least "possibly attributable" to the study agent(s) within 30 days after the administration of the investigational treatment (GPS plus pembrolizumab).

If the study is stopped due to activation of the above rules, the safety data will be examined by the Sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study at large.

5.3.6.2. AML-Specific Dose-Limiting Toxicities

For patients enrolled in the AML arm, the DLT window of observation will be defined by the first 8 weeks from study entry/administration of first galinpepimut-S inoculation.

The occurrence of any of the following toxicities during the first 8 weeks (from the time of administration of the first galinpepimut-S inoculation), if assessed by the investigator to be reasonably possibly related to study drug, will be considered a DLT:

1. Missing > 25% of the doses of investigational agent(s) as a result of drug-related AE during cycle 1 and/or 2
2. Drug-related AE which causes patient to discontinue treatment during cycle 1 and/or 2
3. Grade 5 toxicity
4. Grade 4 non-hematological toxicity (other than laboratory abnormality)
5. Grade 3 non-hematological toxicity (other than laboratory abnormality; exception: fatigue, nausea, emesis, diarrhea, rash, infection, fever, or bleeding unless the event lasts more than 3 days despite optimal care)
6. Grade 3 and 4 non-hematological lab abnormality, if any of the following occurs:
    a. Medical intervention is required
    b. Abnormality persists > 1 week
    c. Abnormality results in drug-induced liver injury
7. Any treatment-related toxicity that causes a greater than 3-week delay in initiation of cycle 2 and/or 3 (the latter cycle being the first one whereby galinpepimut-S and pembrolizumab are co-administered).
8. Development of an immune-related AE (irAE) resulting in withholding of pembrolizumab and initiation of steroids, for example, grade 2 or higher colitis/diarrhea, grade 2 or higher pneumonitis, grade 2 or higher transaminitis, any grade myocarditis (complete list currently shown in Table 5)

Any other toxicities in the AML arm will not be considered dose-limiting.

Staggered Early Enrollment:

To minimize exposing subjects to the risk of potential unknown acute and subacute toxicities of combining HMA with the investigational therapy (pembrolizumab and galinpepimut-S) in the AML arm, the inter-dosing interval between the first two (2) subjects to be enrolled in this study arm will be 12 weeks.

AML-specific DLT assessment and actions will be as follows (unless stopping rules apply):

- Initially up to 6 patients will be enrolled in the AML cohort. If 2 or fewer patients of these first 6 patients have DLTs, enrollment can continue for up to another 6 patients in the AML arm with no dose adjustments made. If DLTs are observed in more than 2 patients of the first 6, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the immediately subsequent administration after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.
- In the next 6 patients (patients 7 to 12), if again, 2 or fewer of these patients have DLTs observed, enrollment can continue. If DLTs are observed in more than 2 of patients 7 to 12, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled, but pembrolizumab will continue as scheduled.
- If DLTs are observed in more than 2 patients of the first 6 (patients 1 to 6) and again in more than 2 patients of the next 6 (patients 7 to 12), the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT. For example, if galinpepimut-S was given on a Q3W schedule before the DLT occurred, it should be given Q6W for the 2 immediately subsequent administrations after the dosing event associated with the DLT, while keeping the pembrolizumab dose and frequency stable.

- If DLTs continue to be observed above 2 per every 6 patients beyond these first 12 patients, and even after the changes in administration of galinpepimut-S, the study will be stopped and the safety data will be examined by the sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study.
- Should a given patient experience any of the above DLTs at any time after the completion of the first cycle of co-administration of galinpepimut-S in combination with pembrolizumab, the time interval between galinpepimut-S doses for the inoculation following the one associated with the DLT will be doubled, but pembrolizumab will continue as scheduled.
- If another DLT occurs in that next cycle, the time interval between galinpepimut-S doses will be doubled for two (2) inoculations following the one associated with the DLT, but pembrolizumab will continue as scheduled.
- If no DLTs re-occur after the above periods of doubly 'spaced out' administrations, then the patient should revert back to the initial GPS Q3W schedule (as per the initial dosing frequency/ investigational agent administration schedule).
- If a DLT occurs after these dose modifications in subsequent cycles, the patient will be discontinued from the study.

The above dose density modifications in response to DLTs is further summarized in the bulleted list of actions below:

- First DLT → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **once thereafter**, i.e. **for 1 additional cycle** → DLT resolution → Return to per protocol schedule of GPS administration
- Second DLT (after reverting to the per protocol schedule) → skip the next GPS inoculation (scheduled for the next cycle, i.e., 3 wks ahead) and administer GPS 6 wks ahead (i.e., 'spread out') **twice thereafter**, i.e. **for 2 additional cycles** → DLT resolution → Return to per protocol schedule of GPS administration

- Third DLT (occurring either after reverting to the per protocol schedule or during the 'spread out' schedule to manage the 2nd DLT above) → Discontinue patient from study.
- N.B.: In all above modifications of the dose density of galinpepimut-S, as all intervals (in weeks) between 2 successive GPS administrations are multiples of three (3) by design, following these rules, co-administration with pembrolizumab is always secured.

Stopping rules (for AML patients):

- Development of any SAEs at least "possibly attributable" to the study agent(s) in 2 out of the first 6 patients in the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.
- The fraction of patients experiencing an SAE at least "possibly attributable" to the study agent(s) exceeds 1/3, at any time during study implementation beyond the first 6 patients.
- Death at least "possibly attributable" to the study agent(s) within 30 days after the administration of the investigational treatment (GPS plus pembrolizumab)
- Development of grade 3 or higher colitis/diarrhea, grade 3 or higher pneumonitis, grade 3 or higher nephritis, grade 3 or higher transaminitis, or any grade myocarditis in 2 out of the first 6 patients in the AML arm of the study. In this case, the upper 90% one-sided CI bound for 2 patients with SAEs within 6 patients would be 66.7%, consistent with an excessive rate of toxicity.
- The fraction of patients experiencing grade 3 or higher colitis/diarrhea, grade 3 or higher pneumonitis, grade 3 or higher nephritis, grade 3 or higher transaminitis, or any grade myocarditis exceeds 40%, at any time during study implementation beyond the first 6 patients in the AML arm.

If the study is stopped due to activation of the above rules, the safety data will be examined by the sponsor in consultation with investigators in order to determine how to proceed or whether to discontinue the study at large.

5.3.6.3. Dose Modification and Toxicity Management Guidelines for Pembrolizumab

5.3.6.3.1. Dose Modification and Toxicity Management for Immune-related AEs (irAEs) Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	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 (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., 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 feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
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	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.

	evidence of β-cell failure			
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 (e.g., 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 (e.g., 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: Guillain-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).				

5.3.6.3.2. 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 6.

Table 6 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 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 ventilator 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 v5.0 (CTCAE) at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.		

Other allowed dose interruptions for pembrolizumab

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

5.3.7. Toxicity Management of Injection-reactions Related to Galinpepimut-S

Expected AEs from study treatment injection (any component of galinpepimut-S, excluding GM-CSF) include local erythema, edema, itching, and persistent induration at the site of injection. These events are usually mild and may appear after each administration of the study treatment. These Grade 1 and Grade 2 local injection site reactions may resolve spontaneously but they can be treated with topical creams (e.g., aloe), analgesics and/or antihistamines as per investigative site guidelines and will not require treatment interruptions or discontinuation.

Local injection site reactions of grade 3 or higher may require antihistamines, non-steroidal anti-inflammatory agents, and/or steroid therapy as per investigative site guidelines. Re-challenge of a patient after a local grade 3 event will need to be discussed with the medical monitor. Premedication with diphenhydramine 50 mg (or equivalent) and/or paracetamol (325 to 1,000 mg) at least 30 minutes prior to the next treatment injection will be required for the re-challenge. If local toxicity of grade 3 or higher persists, the patient will be moved to the off- treatment follow-up period.

Systemic events of grade 3 or grade 4 toxicity that are considered possibly related to study treatment (any component of galinpepimut-S, excluding GM-CSF) should be quickly discussed with the medical monitor. Autoimmune or hypersensitivity reactions to components of the study treatment or skin test antigens are possibilities. Patients who develop events of non-skin related autoimmune disorders or anaphylactic reactions considered possibly related to the study treatment or any of its components (other than

GM-CSF) may require appropriate care with epinephrine, antihistamines, vasopressors, fluids, and/or steroid therapy as per investigative site guidelines. The medical monitor should be contacted, and these patients will be moved to the off- treatment follow-up period.

Toxicity events related to GM-CSF should be discussed expeditiously with the medical monitor and consideration will be made to either allow the patient to continue the study treatment with or without GM-CSF or to move that particular patient to the off- treatment follow-up period. Treatment of GM-CSF related events are to be treated as per investigative site guidelines.

Toxicity will be graded in accordance with CTCAE v5.0 developed by the NCI (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

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5.3.8. Definition of an Overdose of Investigational Agents for This Protocol

For this trial (a fixed-dose regimen), an overdose will be defined as ≥1,000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

No overdose is defined for galinpepimut-S.

5.3.9. Toxicity Management of Known/Expected AEs Associated with the Continuing Use of Hypomethylating Agents (HMAs) in Patients Enrolled in the AML Arm

Dose modifications for HMA-related (known/expected) toxicities -for either azacitidine or decitabine- in AML patients will be based on the respective US Prescribing Information for these products. These documents are included as Appendices 12.1 and 12.2.

5.3.9.1. Toxicity Profile and Dose Modifications for Azacitidine (AML Patients) (Vidaza® US Prescribing Information; Appendix 12.1)

Most common adverse reactions (>30%) of azacitidine administered by the subcutaneous route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. Most common adverse reactions by the IV route also included petechiae, rigors, weakness and hypokalemia.

Adverse reactions most frequently (≥ 2%) resulting in medical/clinical intervention and/or dose modification in patients receiving azacitidine (S.C. or IV Route) are as follows:

- Discontinuation: leukopenia, thrombocytopenia, neutropenia.
- Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
- Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

Dose Modifications:

A. For hematologic toxicity

For patients with baseline (start of treatment) WBC $\geq$ 3.0 x10^9/L, ANC $\geq$ 1.5 x10^9/L, and platelets $\geq$ 75.0 x10^9/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC ($x10^9$/L)	Platelets ($x10^9$/L)	
Less than 0.5	Less than 25	50%
0.5 –1.5	25-50	67%
Greater than 1.5	Greater than 50	100%

For patients whose baseline counts are WBC < 3.0 $x10^9$/L, ANC < 1.5$x10^9$/L, or platelets < 75.0 $x10^9$/L, base dose adjustments on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case continue the current dose.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30-60	15-30	Less than 15
	% Dose in the Next Course		
50 - 75	100	50	33
Greater than 75	75	50	33

If a nadir as defined in the table above has occurred, give the next course 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are greater than 25% above the nadir and rising. If a greater than 25% increase above the nadir is not seen by day 28, reassess counts every 7 days. If a 25% increase is not seen by day 42, reduce the scheduled dose by 50%.

B. For non-hematologic (serum electrolytes and renal) toxicity

If unexplained reductions in serum bicarbonate levels to less than 20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course.

5.3.9.2. Toxicity Profile and Dose Modifications for Decitabine (AML Patients) (Dacogen® US Prescribing Information; Appendix 12.2)

Most common adverse reactions (> 50%) seen during decitabine therapy include neutropenia, thrombocytopenia, anemia, and pyrexia.

Adverse reactions most frequently (≥ 1%) resulting in medical/clinical intervention and/or dose modification in patients receiving decitabine are as follows:

- Discontinuation: thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.
- Dose Delayed: neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.
- Dose Reduced: neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

Dose Modifications:

A. For hematologic toxicity

If hematologic recovery from a previous decitabine treatment cycle requires more than 6 weeks, delay the next cycle of decitabine therapy and reduce decitabine dose temporarily by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks: Delay DACOGEN dosing for up to 2 weeks and reduce the dose temporarily to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.

- Recovery requiring more than 8, but less than 10 weeks: Perform bone marrow aspirate to assess for disease progression. In the absence of progression, delay the decitabine dose up to 2 more weeks and reduce the dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2 /cycle) upon restarting therapy, then maintain or increase dose in subsequent cycles as clinically indicated.

B. For non-hematologic toxicity

Delay subsequent decitabine treatment for any the following non-hematologic toxicities and do not restart until toxicities resolve:

- Serum creatinine $\geq$ 2 mg/dL
- SGPT, total bilirubin $\geq$ 2 x ULN
- Active or uncontrolled infection

5.4. Management of Clinical Supplies

5.4.1. Study Drug Packaging and Storage

Galinpepimut-S will be provided as a sterile, lyophilized powder filled into a 2 mL colorless glass vial that requires reconstitution with SWFI. Galinpepimut-S should be stored at the site at or below –20°C until use.

Montanide will be packaged in 3-mL amber glass vials. The adjuvant should be stored between 15°C and 30°C. This product must not be frozen.

Avoid freezing and thawing of the emulsified product.

Sargramostim (GM-CSF) will be provided in lyophilized form as a 250-µg sterile, white, preservative-free powder that requires reconstitution with sterile water for injection. It should be stored at 2°C to 8°C. For this study, the vial of GM-CSF is intended for single-use only.

Pembrolizumab will be provided by the sponsor as summarized in Table 7.

Table 7 Pembrolizumab Product Description

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4 mL	Solution for Injection

These supplies will be shipped by the Sponsor indirectly via their Drug Supply packaging, distribution, and logistics vendor (Sharp Clinical Services, Phoenixville, PA, USA) to investigative sites in the appropriate packaging to maintain their recommended temperatures. The supplies are to be stored in their original cartons at the recommended temperatures until ready for use. Until dispensed to the patients, these supplies will be stored in a securely locked area, accessible to authorized personnel only.

5.4.2. Test Article Accountability

The investigator or designee will maintain accurate records of receipt for all study treatment, including dates and quantities of study drug(s) received. The study treatment will be used in accordance with the protocol by patients who are under the direct supervision of the investigator. The study treatment will be dispensed only by an appropriately qualified person to patients in the study. Accurate records will be kept regarding when, how much, and to whom study treatment is dispensed and administered (patient-by-patient, dose-specific accounting). Reasons for departure from the expected dispensing regimen, including study treatment lost or accidentally or deliberately destroyed, will be recorded. The investigator or designee will retain all used, unused, or expired study supplies until the study monitor has

confirmed the accountability data and the sponsor has approved return or destruction. All clinical study treatments and/or supplies will either be destroyed by the site per institutional policy, or be returned to SELLAS or its designee for destruction per applicable regulations.

5.4.3. Other Supplies

Additional supplies provided for this study will be described in the study pharmacy manual.

5.4.4. Blinding

This is an open-label study.

5.4.5. Breaking the Blind

Not applicable.

5.5. Treatment Compliance

Every effort should be made to follow the administration schedule for galinpepimut-S and pembrolizumab. If a patient misses a scheduled administration of either the combination or pembrolizumab alone, the drug(s) should be administered as soon as possible thereafter. If the patient is more than one-half the time interval to the next scheduled administration, the patient should skip that preplanned administration and have the next administration on schedule. The disposition of study treatment received by the site, dispensed and administered to the patient, returned to the sponsor, destroyed, lost, etc. must be recorded in the site's pharmacy log.

5.6. Prior and Concomitant Therapy

Any treatments or therapies other than the study treatment, including biologics; blood products; prescription drugs; over-the-counter medications; and complementary or alternative medications including herbal products/supplements, vitamins, and minerals that the patient is

receiving will be documented. Use of all concomitant medications will be recorded in the patient's source document and eCRF. Any changes in concomitant medications will also be recorded in the patient's source document and eCRF within 28 days from such a change.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF and to consult with the study medical monitor if prohibited medications are considered necessary.

The following medications/treatments are prohibited:

- Other investigational agents given within 4 weeks prior to starting study treatment and during the on-treatment portion of the study.
- Systemic glucocorticoids 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 is allowed, in dosing that does not exceed a total of 10 mg daily of prednisone (or equivalent). If systemic corticosteroids are required for treatment of a co-morbid illness during the study, the investigator should confer with the medical monitor.
    - Note: Inhaled steroids are allowed for management of asthma.
- Immunosuppressive therapies are prohibited throughout the on-treatment portion of the study.
- Patients must have received their last dose of chemotherapy within 3 months before receiving study treatment. Any concurrent cytotoxic chemotherapy, radiation therapy, hormonal therapy, immunotherapy, biologic therapy, or other systemic therapy for cancer is prohibited during the on-treatment portion of the study.

- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- 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.

5.7. Rescue Medications and Supportive Care

5.7.1. Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.3.6.3, Table 5. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 5.3.6.3.2, for guidelines regarding dose modification and supportive care.

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

5.8. Diet/Activity/Other Considerations

5.8.1. Meals and Dietary Restrictions Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.8.2. Contraception

Galinpepimut-S and 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. Please refer to Section 6.6 for further details.

Participants 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, participants of childbearing potential must adhere to the contraception requirement (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 study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.8.3. Pregnancy

If a participant inadvertently becomes pregnant while on treatment with either pembrolizumab or galinpepimut-S, the participant will be immediately discontinued from

study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

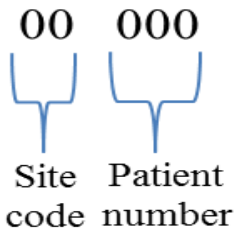
5.8.4. Nursing Women

It is unknown whether one of the components of the investigational therapy, i.e., 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, participants who are breastfeeding are not eligible for enrollment.

6. Study Assessments and Procedures

All patients must sign and date the informed consent before any study-specific procedures are performed. The study will be discussed with the patient and he or she will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF. The patient must also give authorization regarding privacy requirements before any study-related procedures.

Each patient who provides informed consent and meets all of the inclusion criteria and none of the exclusion criteria at Day -3 (Baseline visit) will be enrolled using IWRS and will be assigned a 5-digit number that will be used on patient documentation throughout the study. The first 2 digits of the number will refer to the site code and the last 3 digits will be a patient-specific number at that site. Patient numbers at each site will be assigned in ascending order and numbers will not be omitted or reused.



Refer to Table 8 for the Schedule of Assessments.

Table 8 Schedule of Assessments

Procedures	Screening Period		Open-Label Treatment Period[a]											Safety Follow-up Period	
	Screening	Baseline[b]	Int. 2 WT1-immunizing Inj (Q3 wk)		Subsequent 4 WT1-immunizing Inj (Q3 wk)		Int. 1	Booster Inj Period - A (Q3 wk)		4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)	Booster Inj Period – B (Q12 wk)		Final Pembrolizumab Monotherapy Phase	EOT/ET[c]	Off-treatment
Week			0, 3		6, 9, 12, 15		18	21, 24, 27, 30, 33, 36		[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]	48, 60, 72, 84		87, 90, 93, 96, 99, 102, 105, and 108	30 days after last inj.	Every 3 mnths[c]
Day(s)	-28 to -4	–3[b]	-2	1	-2	1	1	-2	1	1	-2	1	1		
Informed consent	X														
Inclusion/ exclusion	X	X													
Tumor tissue[d]	X														

Procedures	Screening Period		Open-Label Treatment Period[a]											Safety Follow-up Period	
	Screening	Baseline[b]	Int. 2 WT1-immunizing Inj (Q3 wk)		Subsequent 4 WT1-immunizing Inj (Q3 wk)		Int. 1	Booster Inj Period - A (Q3 wk)		4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)	Booster Inj Period – B (Q12 wk)		Final Pembrolizumab Monotherapy Phase	EOT/ET[c]	Off-treatment
Week			0, 3		6, 9, 12, 15		18	21, 24, 27, 30, 33, 36		[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]	48, 60, 72, 84		87, 90, 93, 96, 99, 102, 105, and 108	30 days after last inj.	Every 3 mnths[c]
Day(s)	-28 to -4	–3[b]	-2	1	-2	1	1	-2	1	1	-2	1	1		
Demographics[e]	X														
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical and surgical history	X														
Physical examination[f]	X	X													
ECOG	X	X		X		X	X		X	X		X	X	X	
Vital sign[g]	X	X		X		X	X		X	X		X	X	X	

Procedures	Screening Period		Open-Label Treatment Period[a]											Safety Follow-up Period	
	Screening	Baseline[b]	Int. 2 WT1-immunizing Inj (Q3 wk)		Subsequent 4 WT1-immunizing Inj (Q3 wk)		Int. 1	Booster Inj Period - A (Q3 wk)		4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)	Booster Inj Period – B (Q12 wk)		Final Pembrolizumab Monotherapy Phase	EOT/ET[c]	Off-treatment
Week			0, 3		6, 9, 12, 15		18	21, 24, 27, 30, 33, 36		[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]	48, 60, 72, 84		87, 90, 93, 96, 99, 102, 105, and 108	30 days after last inj.	Every 3 mnths[c]
Day(s)	-28 to -4	–3[b]	-2	1	-2	1	1	-2	1	1	-2	1	1		
Height	X														
Weight	X	X		X		X	X		X	X		X	X	X	
Beta-hCG	X	X													
HIV testing	X														
12-lead ECG	X														
PT, PTT, and INR	X														
Hematology[h]	X			X		X	X		X	X		X	X	X	
Serum chemistry[i]	X			X		X	X		X	X		X	X	X	

Procedures	Screening Period		Open-Label Treatment Period[a]											Safety Follow-up Period	
	Screening	Baseline[b]	Int. 2 WT1-immunizing Inj (Q3 wk)		Subsequent 4 WT1-immunizing Inj (Q3 wk)		Int. 1	Booster Inj Period - A (Q3 wk)		4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)	Booster Inj Period – B (Q12 wk)		Final Pembrolizumab Monotherapy Phase	EOT/ET[c]	Off-treatment
Week			0, 3		6, 9, 12, 15		18	21, 24, 27, 30, 33, 36		[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]	48, 60, 72, 84		87, 90, 93, 96, 99, 102, 105, and 108	30 days after last inj.	Every 3 mnths[c]
Day(s)	-28 to -4	–3[b]	-2	1	-2	1	1	-2	1	1	-2	1	1		
TSH, FT4, and T3 or FT3	X			X		X	X		X	X		X	X	X	
Urine test[j]	X			X		X	X		X	X		X	X	X	
HLA typing[k]	X														
Cytogenetics and molecular analysis[l]	X														
Bone Marrow biopsy[m]	X					X[w]	X		X[x]	X[y]		X[z]		X	

Procedures	**Screening Period**		**Open-Label Treatment Period[a]**											**Safety Follow-up Period**	
	Screening	**Baseline[b]**	**Int. 2 WT1-immunizing Inj (Q3 wk)**		**Subsequent 4 WT1-immunizing Inj (Q3 wk)**		**Int. 1**	**Booster Inj Period - A (Q3 wk)**		**4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)**	**Booster Inj Period – B (Q12 wk)**		**Final Pembrolizumab Monotherapy Phase**	**EOT/ET[c]**	**Off-treatment**
Week			**0, 3**		**6, 9, 12, 15**		**18**	**21, 24, 27, 30, 33, 36**		**[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]**	**48, 60, 72, 84**		**87, 90, 93, 96, 99, 102, 105, and 108**	**30 days after last inj.**	**Every 3 mnths[c]**
Day(s)	**-28 to -4**	**–3[b]**	**-2**	**1**	**-2**	**1**	**1**	**-2**	**1**	**1**	**-2**	**1**	**1**		
Multigene MRD analysis[n]	X						X		X[x]	X[y]		X[z]		X	
Immunologic Marker assessment[o]		X				X[w]	X		X[aa]	X[y]		X[z]		X	
Biopsies of malignant tissue deposit[p]	X						X		X[x]	X[t]		X[z]		X	
CT or MRI[q]	X					X[w]	X		X[aa]	X[bb]		X[z]		X	

Procedures	**Screening Period**		**Open-Label Treatment Period[a]**											**Safety Follow-up Period**	
	Screening	**Baseline[b]**	**Int. 2 WT1-immunizing Inj (Q3 wk)**		**Subsequent 4 WT1-immunizing Inj (Q3 wk)**		**Int. 1**	**Booster Inj Period - A (Q3 wk)**		**4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)**	**Booster Inj Period – B (Q12 wk)**		**Final Pem-brolizumab Mono-therapy Phase**	**EOT/ET[c]**	**Off-treatment**
Week			**0, 3**		**6, 9, 12, 15**		**18**	**21, 24, 27, 30, 33, 36**		**[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]**	**48, 60, 72, 84**		**87, 90, 93, 96, 99, 102, 105, and 108**	**30 days after last inj.**	**Every 3 mnths[c]**
Day(s)	**-28 to -4**	**–3[b]**	**-2**	**1**	**-2**	**1**	**1**	**-2**	**1**	**1**	**-2**	**1**	**1**		
Enrollment to study[r]		X													
GM-CSF SC[s]			X	X	X	X		X	X		X	X			
Assess local immunization site		X		X		X			X			X			
Galinpepimut-S[t]				X											
Galinpepimut-S with pembrolizumab						X			X			X			

Procedures	Screening Period		Open-Label Treatment Period[a]											Safety Follow-up Period	
	Screening	Baseline[b]	Int. 2 WT1-immunizing Inj (Q3 wk)		Subsequent 4 WT1-immunizing Inj (Q3 wk)		Int. 1	Booster Inj Period - A (Q3 wk)		4 Series of Subsequent Intervals (2-4, 5-7, 8-10, and 11-13)	Booster Inj Period – B (Q12 wk)		Final Pembrolizumab Monotherapy Phase	EOT/ET[c]	Off-treatment
Week			0, 3		6, 9, 12, 15		18	21, 24, 27, 30, 33, 36		[39, 42, 45], [51, 54, 57], [63, 66, 69], [75, 78, 81]	48, 60, 72, 84		87, 90, 93, 96, 99, 102, 105, and 108	30 days after last inj.	Every 3 mnths[c]
Day(s)	-28 to -4	–3[b]	-2	1	-2	1	1	-2	1	1	-2	1	1		
30-minute post injection observation				X	X	X		X	X		X	X			
Pembrolizumab administration alone							X			X			X	X	
Adverse events[u]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of survival[v]				X		X	X		X	X		X	X	X	X

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; GM-CSF, granulocyte-macrophage colony-stimulating factor (sargramostim); INR, international normalized ratio; IV, intravenous; MRI, magnetic resonance imaging; MRD, minimal residual disease; mnths, months; PT, prothrombin time; PTT, partial thromboplastin time.

a. To assess progression-free survival, relapse must be documented, and the following procedures performed: concomitant medication, AEs, ECOG performance status, blood samples (hematology, serum chemistry, immune/exploratory correlates), and evaluation of clinical endpoints. For AML patients that have relapsed, the relapse visit will also include BM aspiration. For non-progressors: At the time of progression/relapse documentation, an additional 'relapse visit' will be performed; refer to Section 6.1.5.
b. At the baseline visit (Day −3), all pretreatment screening procedures and assessments must be completed, review of inclusion/exclusion criteria (including specific tumor histologic type verification, [e.g., TNBC]), and review of laboratory and tissue pathology results confirmed prior to enrollment and the first GM-CSF injection.
c. Patients who complete the study treatment period or patients who discontinue early (if they have received at least 1 treatment injection) will enter an off-treatment follow-up period to assess progression-free survival and overall survival. A follow-up phone call for serious adverse events will occur 90 days after the last dose of pembrolizumab OR 30 days following cessation of study treatment if the patient begins a new anticancer therapy, whichever is earlier. If the patient begins a new anticancer therapy, this must be reported by the investigator. If a patient is confirmed to have recurrent/refractory/relapsed disease after completion of a relapse visit, the patient is to return to the site within 30 days after their last treatment injection to complete EOT/early termination visit procedures.
d. Retrieval of archival specimens (paraffin block sections) of tumor tissue (for solid tumors) or bone marrow (for AML) for WT1 IHC testing. Biopsy of current tumor tissue (for solid tumors) or bone marrow (for AML) for WT1 IHC. For CRC only: additionally, collection of current tissue sample for microsatellite stability analysis.
e. Demographics will include sex, age, race and ethnicity.
f. Abnormal physical examination findings identified at the screening visit will be followed until resolution or stabilization. Any ongoing findings (after study enrollment) should be recorded as pretreatment adverse events (AEs) and will be graded by Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

g. Vital will include body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate.

h. The hematology assessment will include a complete blood count (CBC) with differential and platelet count. These samples will be collected for processing by the central laboratory. Samples must be collected before study treatment administration. For abnormal complete blood count results, a manual differential is required. Specifically for AML patients, if the differential is suggestive of abnormal or immature cells and a possible relapse, a bone marrow biopsy must be performed as part of a scheduled relapse visit. See the laboratory manual for more information.

i. The serum chemistry assessments will include sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, total protein, albumin, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. These samples will be collected for processing by the central laboratory. Samples must by collected before study treatment administration. Calculated Creatinine Clearance (CrCl) must be assessed during the screening period to determine eligibility. See the laboratory manual for more information.

j. Urine dipstick testing will be performed locally at the site.

k. Patients will provide any historical documentation of HLA type at the pretreatment screening visit. The majority of patients will not have such information available and must undergo HLA typing assessment at participating sites.

l. ***For AML patients ONLY***: provide historical documentation of cytogenetic and molecular analyses results (from initial diagnosis) at the pretreatment screening visit. Only patients with abnormal karyotype at initial diagnosis will require to repeat karyotype plus/minus fluorescence in situ hybridization (FISH) at pretreatment screening in this study. Full molecular analysis (i.e., FLT3-ITD and NPM1 mutations, etc.) will also be performed on bone marrow biopsy samples collected during pretreatment screening in all AML patients.

m. ***For AML patients ONLY***: a bone marrow aspiration and biopsy is required during pretreatment screening to confirm morphologic partial response (PR) or stable disease (SD) status, for MRD analysis, and for cytogenetic and molecular analyses as defined in footnote k. Additional bone marrow biopsies are required as shown per schedule, as well as at the end-of-treatment/early termination visit to evaluate progression and MRD. If a peripheral blood differential result (including manual differentiation) at any study visit is suggestive of abnormal or immature cells and a possible relapse, a bone marrow biopsy must be performed as part of a scheduled AML relapse visit. If the bone marrow biopsy confirms relapse, the patient will be discontinued from the study and will need to return to the site 0 to 30 days after their last treatment injection for end-of-treatment/early termination procedures. The bone marrow aspiration performed as part of the scheduled relapse visit will serve as bone marrow aspiration procedure required at the end-of-treatment/early

termination visit. A bone marrow biopsy must be collected if an adequate aspiration is not attainable. Refer to the laboratory manual for collection and processing these samples.

n. ***For AML patients ONLY***: Analysis of MRD will be performed on samples of peripheral blood and will be evaluated by molecular analysis of transcripts. Peripheral blood samples will be collected from patients according to the schedule shown. Samples must be collected before study treatment administration. Refer to the laboratory manual for collection and processing of samples.

o. Peripheral blood samples for immunologic response (IR) assessment will be collected from a large subset of patients enrolled in each of the 5 arms of the study at select sites as per the schedule shown. The study is aiming to analyze IR profile in at least 50% of the enrolled patients. Samples must be collected before study treatment administrations. Refer to the laboratory manual for collection and processing these samples.

p. Biopsies of malignant tissue deposit (or bone marrow, for AML patients) will be performed according to the schedule shown in a subset of patients at select sites. These tissue specimens will be used to study the presence and kinetics of host immunocytes infiltrating the above tissues, as well as the expression of key markers of immune biological significance in the tumor microenvironment. All biopsies are in principle mandatory, as long as the tumor deposits are technically accessible and such biopsies can be conducted safely.

q. For solid tumors only: CT or MRI staging assessment (both per RECIST and iRECIST).

r. Prior to contacting IWRS to enroll a patient into the study and obtaining a patient number, the following must be reviewed and verified: inclusion/exclusion criteria (including specific tumor histologic type verification, [e.g., TNBC]), laboratory and tissue pathology.

s. GM-CSF will be administered 2 days before and on the day of each galinpepimut-S administration. A GM-CSF dose of 70 µg will be injected subcutaneously at the same anatomical site as the planned subsequent galinpepimut-S injection (to be given during the same cycle of therapy). Before injection, study staff should assess the immunization site. On Day −1, patients will remain in the clinic for approximately 30 minutes following receipt of GM-CSF to monitor for any adverse reactions. Blood samples will be collected before study treatment administration.

t. Immediately after the patient receives the GM-CSF injection, patients are to receive galinpepimut-S injected SC in the same anatomical location as the GM-CSF injection. The injection site should be on the arm, leg, or torso of the patient, and should be positioned at least 5 cm away from the previous site of study treatment injection.

u. Adverse event reporting begins from the time of signing the ICF to 30 days after the last injection of any study treatment (GPS/placebo or pembrolizumab). Adverse events collected before the first injection of GM-CSF will be reported as “pre-WT1 AEs”. All AEs will be graded by

CTCAE, Version 5.0. A follow-up phone call for serious adverse events will occur 90 days after the last dose of pembrolizumab or 30 days following cessation of study treatment if the patient begins new anticancer therapy, whichever is earlier. If the patient initiates new anticancer therapy, this must be reported by the investigator.

v. Patients who complete the study, or who discontinue because of any reason other than recurrent/refractory/relapsed disease will return to the site 30 days after their last injection for final safety follow-up and completion of EOT/ET visit.

w. Only to occur at Week 9.

x. Only to occur at Week 36.

y. Only to occur at Week 54.

z. Only to occur at Weeks 72 and 84.

aa. Only to occur at Weeks 27 and 36.

bb. Only to occur at Weeks 45, 54, and 63.

6.1. Study Visits

6.1.1. Screening Period and Enrollment

Informed consent must be obtained before any study-related procedures are conducted. All study-specific screening procedures must be completed within 28 days (refer to Table 8 for screening procedures). At the baseline visit (Day −3), all pretreatment screening procedures/assessments must be completed and laboratory results confirmed prior to enrollment and the first injection of GM-CSF.

If a patient does not meet inclusion/exclusion criteria within 28 days of signing the ICF, the patient will be considered a screen failure and may be allowed to re-screen with a newly signed ICF up to 2 times.

6.1.2. Open-Label Treatment Period

Refer to Section 5 (Study Treatments) and Table 8 (Schedule of Assessments) for further details.

6.1.3. End of Treatment/Early Termination Visit

Patients who complete the protocol-specified study injections or scheduled study visit evaluations, or who discontinue because of any reason other than recurrent/refractory/relapsed disease will return to the site 30 days after their last injection for final safety follow-up and completion of the EOT/early termination procedures.

6.1.4. Safety Follow-up Period

Patients who complete the study treatment period or discontinue early (if they have received at least 1 treatment injection) will enter an off-treatment follow-up period to assess progression-free survival and overall survival. A follow-up telephone call for serious adverse events will occur 90 days after the last dose of pembrolizumab or 30 days following cessation of study treatment if the patient begins new anticancer therapy, whichever is

earlier. If the patient initiates new anticancer therapy, this must be reported by the investigator. Patients will be followed in accordance with standard guidelines, which suggest regular assessments every 3 months until study closure, defined as up to 2 years and 6 weeks, i.e., 111 weeks, after the first galinpepimut-S administration given to the last patient enrolled into the study (which corresponds to up to 2 years after the first injection of pembrolizumab).

6.1.5. Relapse Visit

In addition to the SOA above, one additional series of assessments will be performed at the time of tumor (or leukemia) relapse. Indeed, to assess PFS, it is important to document disease relapse. At the time of the "relapse visit", the following assessments will be performed:

- Collect and update concomitant medication information
- Collect and update AEs
- Obtain ECOG performance score
- Obtain vital signs and document weight
- Collect blood samples for the central laboratory
    - Hematology (CBC with differential and platelet count)
    - Serum chemistry
    - Immune/exploratory correlates
- Evaluate clinical endpoints

For AML patients in specific, PB differentials from CBCs collected during every visit will be used to determine initially if the patient has relapsed, as defined by loss of CR status (if previously achieved) or further progression beyond initially achieved PR. For abnormal CBCs, a manual differential is required. If the differential is suggestive of abnormal or

immature cells and a possible relapse, a BM aspiration must be performed as part of a scheduled relapse visit to confirm the diagnosis of recurrent/relapse/refractory AML. A BM biopsy must be performed if an adequate aspiration is not attainable. In patients with AML who achieve CR status while on investigational therapy (galinpepimut-S plus pemrolizumab – administered on top of their continuing HMA regimen), relapse (post-CR) will be defined as a reappearance of leukemic blasts in the PB or >5% blasts in the BM not attributable to any other cause (e.g., BM regeneration after chemotherapy [Cheson et al, 2003]). If relapse is confirmed, the patient should be discontinued from the on-treatment portion of the study due to recurrent/refractory/relapsed AML and will need to return to the site 0 to 30 days after their last treatment injection for final safety follow-up and completion of the EOT/early termination visit procedures. The BM aspiration performed as part of the scheduled relapse visit will serve as BM aspiration procedure required at the EOT/early termination visit.

Once EOT/early termination visit procedures have been completed, the physician can choose to treat the documented recurrent/refractory/relapsed disease with any subsequent therapy they choose. The patient will be moved to the off- treatment follow-up period and will be followed only for AEs and OS.

6.1.6. Unscheduled Visits

As appropriate, assessments at any unscheduled visit should follow the assessments at the closest weekly/monthly/quarterly visit.

6.2. Efficacy Assessments

Signal response for each a priori statistically defined clinical outcome (ORR per RECIST 1.1) for all patients enrolled in the solid tumor arms of the study or other appropriate instruments scales, such as attainment of morphologic CR in patients enrolled in the AML arm. In addition to RECIST 1.1, all scans will be read according to iRECIST immune response consensus guideline (Seymour et al, 2017) to ensure that patients are not discontinued from therapy due to the phenomenon of tumor “pseudoprogression”, and clinical decisions will be based on iRECIST (Hodi et al, 2016). ORR per iRECIST will be an exploratory endpoint of this study.

6.3. Exploratory Assessments

Assessment of tumor response in solid tumor patients by iRECIST, as well as estimation of the rate of achievement of MRD negativity in AML patients are exploratory endpoints in this study.

All patients will be followed and assessed for PFS and OS, as per the schedule of assessments and using the ITT principle.

As an exploratory evaluation, this study will assess the effect of the study treatment on readouts of immunologic tests in PB samples (see below), as well as presence and density of immune cell infiltrates within the tumor stroma (or BM in AML patients) using at least one post-therapy tumor biopsy (and comparing the findings with those at baseline, i.e., prior to initiation of treatment).

In more detail:

In peripheral blood:

The following parameters will be tested:

- *Galinpepimut-S -relevant immune resonse-relevant:*
- *WT1 peptide--specific CD8 and CD4 cell frequencies:*
    - Cell frequencies (absolute cell abundance/numbers/microliter of blood) of host CD8 and CD4 cells that react with increased production of intracellular interferon-γ as detected by intracellular cytokine staining (ICS) after ex vivo re-stimulation (Pinella-Ibarz et al, 2006; Gomez-Nunez et al, 2006; Maslak et al, 2010) with the following peptides:
        - WT1A1 (heteroclitic)
        - WT1A (cognate native of the one above)

- 122A1 (heteroclitic)
- 122A (cognate native of the one above)
- 331 (native)
- 427 (native)

- *Complete lymphocyte population panel (non-antigen-specific)*

  Cell frequencies (absolute cell abundance/numbers/microliter of blood) - for each patient at each timepoint of collection, as follows:

  - Naïve T cells: CD45RA+CD45RO-CCR7+CD62L+CD57-
  - Central memory T cells: CD45RA-CD45RO+CCR7+CD62L+CD57-
  - Effector memory T cells: CD45RA-CD45RO+CCR7-CD62L-CD57+
  - Total effector cells: CD45RA+CD45RO-CCR7-CD62L-CD57+
  - Tregs: FoxP3+, CD25+, PD1, ICOS
  - Myeloid-derived suppressor cells (MDSC's):
  - PMN-MDSC's: CD14-CD11b+CD15+(or CD66b+) and
  - M-MDSC's: CD11b+CD14+HLA-DRlow/−CD15−
    - Thus, the following antibody "gates" would have to be utilized in methodology selected (see Laboratory Manual): CD3, CD4, CD8, CD45RA or CD45RO, CD57, and CCR7 or CD62L or CD27, FoxP3, CD25, PD1, ICOS, CD14, CD11b, CD15; HLA-DR

- **In tumoral biopsy samples (TBx):**

- *Galinpepimut-S -relevant*
- The following parameters will be tested:

- Intratumoral CD8 and CD4 (cells within tumor stroma versus surrounding the tumor proper) (Arlen and Arlen, 2013)
- MDSC, T-regulatory cells (Treg), and tumor-associated macrophages (TAMs)

General (non-antigen-specific) immunodynamics

- PDL1 expression and Interferon-γ tissue inflammatory gene expression 'signature' assessment

Genetic (DNA) analyses

- The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability, etc.). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a "hyper-mutated" state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome wide approaches will be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.
  - Specifically for CRC patients:
    - MSI will be evaluated in all CRC patients enrolled in this study, as this is an important biomarker for this type of cancer.

6.4. Safety Assessments

Patients will be monitored for AEs and will undergo safety assessments including vital signs and weight, ECOG performance status, and clinical laboratory testing, which will include CBC with differential and platelet count, serum chemistry assessment, and urine dipstick test.

6.4.1. Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study treatment or their clinical significance. If AEs occur, the first concern will be the safety of the study patients.

Any abnormal laboratory test results (hematology, clinical chemistry, or urine dipstick) or other abnormal finding or safety assessments (e.g., vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator will be graded by CTCAE v5.0 criteria and are to be recorded as AEs or SAEs.

Adverse event monitoring will occur from the time of signing the ICF to 30 days after the last injection of study treatment.

6.4.1.1. Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study and does not necessarily have to have a causal relationship (association) with this treatment. An AE can therefore be any unfavorable or untoward sign, symptom, disease, syndrome, intercurrent illness, or abnormal laboratory finding that emerges or worsens relative to the patient's pretreatment baseline, whether or not it is considered to be related to the investigational product.

A TEAE is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.

An SAE is any AE at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Constitutes an important medical event (i.e., the AE did not meet any of the above serious criteria but based on appropriate medical judgment, may have jeopardized the patient or required medical or surgical intervention to prevent one of the serious outcomes listed in these criteria)

6.4.1.2. Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF until 30 days after the last study treatment injection. Adverse events collected before injection of study treatment will be reported as pretreatment AEs and those collected after the first injection of GM-CSF and throughout the study will be reported as TEAEs. Serious AEs that occur more than 30 days after the last dose of study treatment need not be reported unless the investigator considers them related to study treatment. Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications) or therapies. Patients will also be instructed to contact the investigator at any time after beginning study treatment if any signs or symptoms develop.

In addition to patient observations, AEs identified from any study data (e.g., laboratory values), or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

All AEs must be documented on the AE pages of the eCRF and in the patient's medical record. The following attributes must be assigned: (1) description; (2) dates of onset and resolution; (3) severity (per CTCAE v5.0); (4) assessment of relatedness to the study medication (unrelated, possible, probable, definite); (5) "serious" criteria if applicable (see Section 6.4.1.3 on how to report SAEs); (6) action taken; and (7) outcome (recovered/resolved, not recovered/resolved, recovered/resolved with sequelae, ongoing, or death). The investigator will actively solicit this information and assess the AEs in terms of severity and relationship to study treatment. The investigator will treat the patient as medically required until the AE either resolves or becomes medically stable. Treatment for AEs may extend beyond the duration of the study. The investigator will record treatment and medications required for treatment on the appropriate eCRF(s). In the event that a patient is withdrawn from the study because of an AE or SAE, it must be recorded on the Termination eCRF as the reason for discontinuation. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

6.4.1.3. Reporting Adverse Events

AE, SAEs, and other reportable safety events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome.

Any AE that meets SAE criteria (Section 6.4.1.1) must be reported to SELLAS (via its CRO, i.e., Cancer Insight, LLC, San Antonio, TX, USA) immediately (i.e., within 24 hours) after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

E-mail: safety@prevailinfoworks.com

Fax Number: +1-888-400-5240

Phone Number: +1-888-846-7268

In addition, the investigator must record the SAE in the appropriate AE section of the eCRF within 24 hours of learning of the event. The eCRF should be completed as much as possible, but should not be held until all information is available if obtaining that information will take longer than 24 hours. Additional information and/or corrections should be submitted as they are obtained and reported in the eCRF as soon as possible.All deaths, whether considered study related or not, must be reported immediately to SELLAS and its designee with a copy of the autopsy report and the death certificate provided, if available. All initial suspected unexpected serious adverse reaction (SUSAR) events that are life-threatening or result in death will also be reported to the site's IRB/IEC of record within 7 calendar days and follow up within 15 calendar days. All other SUSAR's experienced will be reported to the IRB/IEC within 15 calendar days. If the SUSAR results in death or is life threatening, a SUSAR report will be submitted initially to the regulatory authority within 7 calendar days and follow up within 15 calendar days. All other SUSAR's must be reported to the regulatory authority within 15 days. It is the responsibility of the contract research organization (CRO, i.e., Cancer Insight, LLC) to report all SUSARs to the appropriate ethics committees, investigators, and sponsor. It is the responsibility of SELLAS to report all SUSARs to the appropriate regulatory authority (FDA) in accordance with the Code of Federal Regulations.

The site may contact the medical monitor with any questions at any time. Refer to the cover page for medical monitor contact information. Reports of all (expected or unexpected) SAEs must be reported to the CRO (Cancer Insight, LLC) via email – clinical@cancerinsight.com and to Prevail Pharmacovigilance - safety@prevailinfoworks.com. In accordance with the FDA regulations and the International Council on Harmonisation (ICH) guidelines, investigators will be notified of the occurrence of new, serious, unexpected AEs associated with the use of the study medication (i.e., there is a reasonable possibility that the AE may

have been caused by the drug) via a written report. Expedited SAEs will be reported to all study investigators via a "Dear Doctor" letter sent by SELLAS, or its designee. It is the responsibility of the investigator to promptly inform the relevant IRB of record of these new AEs/risks to patients, in accordance with 21 Code of Federal Regulations (CFR) 312.66.

6.4.1.4. Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The investigator must make a clinical determination of the intensity and severity of each AE by using the NCI CTCAE v5.0. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following guideline:

Grade 1: Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life threatening or debilitating: consequences; urgent intervention indicated

Grade 5: Death

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.1.5. Assessment of Causality

As part of the AE documentation process, investigators are required to assess whether there is a reasonable possibility that study medications caused or contributed to an AE. This is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The following general guidance for assessment of causality may be used:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

Causality will be assessed for GM-CSF and study treatments separately when the AE or SAE is clearly related to the administration of GM-CSF.

6.4.1.6. Exceptions

Progression of the cancer under study is not considered an adverse event.

The following events will not be reported as AEs or SAEs:

- Relapse or recurrence of baseline tumor type
- Hospitalization for a procedure for protocol-related investigations
- Hospitalization for an elective treatment or procedure for a pre-existing condition unrelated to the study
- Hospitalization or prolongation of hospitalization for social or practical reasons

Relapse or recurrence of a patient's cancer will be documented on forms provided to the site and filed in the patient's chart. The patient will be discontinued from the on-treatment portion of the study, and moved to the off-treatment follow-up period. Any therapy initiated for the treatment of the relapse will be documented.

6.4.1.7. Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

For SAEs, the investigator will follow the patient until the SAE resolves, returns to baseline condition or stabilization, or is determined to be permanent, whichever occurs first. Serious AEs that are ongoing at the time of clinical database closure will be recorded as ongoing on the eCRF page. A follow-up phone call for SAEs will occur 90 days after the last dose of pembrolizumab or 30 days following cessation of study treatment if the patient begins new anticancer therapy, whichever is earlier. If the patient initiates new anticancer therapy, this must be reported by the investigator.

6.4.1.8. Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 5.3.8. - Definition of an Overdose for this Protocol, which is not associated with clinical symptoms or abnormal laboratory results.

   N.B.: No overdose is defined for galinpepimut-S.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3× the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is greater than or equal to 2× ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

6.5. Safety Monitoring Committee

Not applicable.

6.6. Pregnancy in Partners of Male Patients

Sexually active male patients are required to use a medically acceptable form of birth control while receiving study treatment and for a period of 4 months following the last study treatment injection. It is unknown whether galinpepimut-S affects the sperm or could be transmitted to the patient's partner during sexual activity. The effect of galinpepimut-S on the fetus is unknown. If a male patient's partner becomes pregnant, the pregnant partner will be requested to sign a pregnant partner consent form. The pregnancy will be followed-up to determine the outcome (including complications, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child. The occurrence of pregnancy and the outcome of any pregnancy in a partner of a patient treated with galinpepimut-S must be reported to SELLAS (via its CRO, Cancer Insight, LLC) and to the pertinent IRB.

Any partner pregnancy that is brought to the site investigator's attention after the patient has completed the study with a timeframe of pregnancy that coincides with the study treatment period or within 4 months following the last study treatment injection or that has an outcome (such as a miscarriage) considered by the site investigator as possibly related to the study treatment must be promptly reported to SELLAS.

6.7. Laboratory Analyses

Laboratory analyses are provided in Table 9 and detailed below.

Blood samples will be drawn for coagulation (INR, PT, PTT), hematology (CBC with differential and platelet count), serum chemistry (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, total protein, albumin, glucose, total bilirubin, alkaline phosphatase, AST, ALT, and lactate dehydrogenase), and thyroid function (TSH [thyroid stimulating hormone], FT4 [free thyroxine], and T3 [triiodothyronine] or FT3 [free triiodothyronine]) and will be sent to the central laboratory for processing.

The urine dipstick test will be performed locally at the site.

For abnormal CBC results, a manual differential is required. Specifically for AML, if the differential is suggestive of abnormal or immature cells and a possible relapse, a BM biopsy must be performed as part of a scheduled relapse visit. See the laboratory manual for more information.

For serum chemistry, calculated creatinine clearance (CrCl) must be assessed during the screening period to determine eligibility. See the laboratory manual for more information.

WT1 IHC will be performed locally and is widely available at all surgical pathology laboratories; to further ensure expertise and consistency, sites will be selected based on experience and will have a designated sub-investigator pathologist trained on the interpretation of WT1 staining. For more details on WT1 IHC, please refer to Section 4.1.1., subheading 4 (b). of this protocol.

Table 9 Laboratory Analyses

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelet count, RBC count, RBC distribution, width, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC Not reported to sites: MCH, MCHC, MCV, MPV
Coagulation	INR, PT, PTT
Serum Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium
Liver Function	ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin
Renal Function	BUN, creatinine
Serum pregnancy	Serum β-hCG
Thyroid Function	T3 or FT3, FT4, TSH
Other	LDH, total protein, glucose
Urinalysis	Dipstick (performed locally at site)

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, β -hCG = beta-human chorionic gonadotropin, BUN = blood urea nitrogen, FT3 = free triiodothyronine, FT4 = free thyroxine, INR= international normalized ration, LDH = lactate dehydrogenase, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MPV = mean platelet volume, PT = prothrombin time. PTT = partial thromboplastin time, RBC = red blood cells, T3 = triiodothyronine, TSH = thyroid stimulating hormone, WBC = white blood cells

6.8. Tumor Imaging and Assessment of Disease

Tumor assessments will be performed by the investigators based on both modified RECIST 1.1 and iRECIST. The former will be used for assessment of the primary endpoint or the trial

(in the solid tumor arms), which is ORR; the latter is an exploratory endpoint. Treatment decisions by the investigator will be based on iRECIST. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans from this study will be accessible in the event it may be requested for them to be submitted central review. If it is decided that central review might be warranted, images acquired for tumor assessments will be sent to an imaging core laboratory for archiving and potential independent analysis.

The process for image collection can be found in the Site Imaging Manual (SIM).

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a patient throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Imaging should include the chest, abdomen, and pelvis.

For TNBC patients, bone scans are also required for patients with a history of bone metastases and/or for those patients with new bone pain.

6.8.1. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of trial treatment or date of allocation. The site study team must review screening images to confirm the patient has measurable disease per RECIST 1.1.

6.8.2. Tumor Imaging During the Study

For solid tumors only, the first on-study imaging assessment should be performed at Week 9 Day 1 ± 7 days) from the date of enrollment. Subsequent tumor imaging should be performed at Weeks 18, 27, 36, 45, 54, 63, 72, and 84 (Day 1 ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Patients will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Patients who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 6.8.5), disease progression should be confirmed by the site 4 to 8 weeks after.

6.8.3. End of Treatment and Follow-up Tumor Imaging

For patients who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For patients who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For patients who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging every 3 months until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.8.4. RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

6.8.5. iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, patients should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix **12.6.**
This allowance to continue treatment despite initial radiologic PD takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should be archived for potential retrospective Blinded Independent Central Review (BICR).

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

If a patient has confirmed radiographic progression (iRECIST confirmed progressive disease [iCPD]) as defined in Appendix . study treatment should be discontinued; however, if the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Appendix

A description of the adaptations and iRECIST process is provided in Appendix , with additional details in the iRECIST publication > 6 eymour et al, 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 10 and illustrated as a flowchart in Figure .

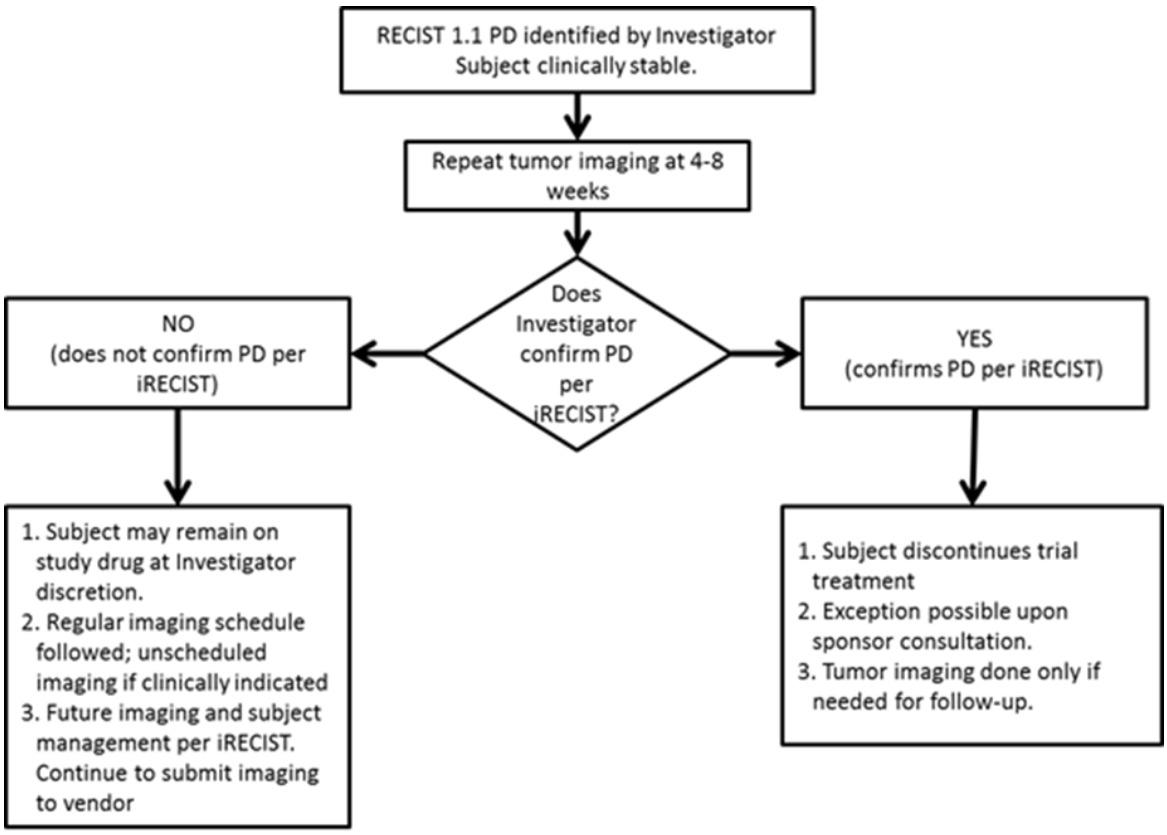
Table 10 Imaging and Treatment after First Radiological Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Figure 14 **Imaging and Treatment for Clinically Stable Patients Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by Investigator**



7. Statistical and Analytical Plan

7.1. Primary Efficacy Endpoints

The primary efficacy endpoints are the safety and tolerability of the combination and ORR within each tumor-specific cohort.

7.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are TTR, time to next treatment and DOR.

7.3. Exploratory Endpoints

The exploratory endpoints are WT1-specific immune response dynamics in PB, select general immunodynamics assessments (in PB and tissue samples, as applicable), genomic testing (including MSS/MSI assessment for CRC) in tissue samples, as well as OS, and PFS.

7.4. Sample Size Calculations

Approximately 90 patients will be enrolled in the study. The planned number of patients within each tumor-specific cohort is as follows: CRC (N = 20), OvC (N = 20), SCLC (N = 20), TNBC (N = 15), and AML (N = 15). This study uses a Bayesian monitoring approach to guide decision-making using data on the primary efficacy endpoint (ORR) within each tumor-specific cohort. If the data provide high confidence that the true ORR (or rate of CR, incl. CRi/CRp, in AML patients) exceeds a minimal clinically meaningful level, then the results would support continued development (a “Go” decision) for that cohort. If the data suggest that the true ORR is unlikely to meet the desired level of clinical activity, then the results would support a decision to halt further continuation of accrual (a “Stop” decision) for that cohort. Definitions of the decision boundaries can be found in Section 7.6.6. Results that do not meet either the Stop or Go criteria are said to be in the consider zone, where determination of the next course of action will be guided by additional information such as secondary endpoints or external data on similar compounds. This

approach is based on the decision-making framework described in Lalonde et al, 2007 and Frewer et al, 2016.

The minimal clinically meaningful level is defined by the "lower reference value" (LRV), and the desired level of clinical activity is defined by the "target value" (TV). The LRV and TV for each tumor type are determined by medical opinion, evidence from the literature, or data from other compounds developing in the same area. These values are as follows: CRC LRV=10%, TV=20%; OvC LRV=10%, TV=20%; SCLC LRV=30%, TV=40%; TNBC LRV=15%, TV=25%; AML LRV=15%, TV=25%.

Enrollment in a cohort may be stopped for futility prior to reaching the planned sample size if there is a high predicted probability of a Stop decision at the planned sample size. Enrollment in a cohort may be increased by approximately 10 additional patients beyond the planned sample size if the sponsor determines that further data on the primary or secondary endpoints is needed to clarify the efficacy signals for a Go/No-Go decision.

Performance of the study design is evaluated on the basis of the probability of entering each decision zone for given true ORR values at the planned sample size within each cohort. Based on the performance characteristics summarized in Table 11 through Table 13, the sample sizes are adequate to address the study's objectives.

Table 11 Statistical Design Performance for CRC or OvC Cohorts of 20 Patients

	Probability of Making Each Decision for a Given True ORR		
True ORR	Go (%)	Consider (%)	Stop (%)
20% (TV)	59	34	7
15%	35	47	18
10% (LRV)	13	48	39

CRC = colorectal cancer; ORR = overall response rate; OvC = ovarian cancer; LRV = lower reference value; TV = target value

Table 12 Statistical Design Performance for SCLC Cohort of 20 Patients

	Probability of Making Each Decision for a Given True ORR		
True ORR	Go (%)	Consider (%)	Stop (%)
40% (TV)	58	29	13
35%	40	36	25
30% (LRV)	23	36	42

ORR = overall response rate; LRV = lower reference value; SCLC = small cell lung cancer; TV = target value

Table 13 Statistical Design Performance for TNBC and AML Cohorts of 15 Patients

	Probability of Making Each Decision for a Given True ORR		
True ORR	Go (%)	Consider (%)	Stop (%)
25% (TV)	54	38	8
20%	35	48	17
15% (LRV)	18	50	32

AML = acute myeloid leukemia; ORR = overall response rate; LRV = lower reference value; TNBC = triple negative breast cancer; TV = target value

Calculations and simulations to determine decision boundaries and performance characteristics were performed using version 3.3.3 of the R software package (R Core Team).

7.5. Analysis Sets

- The full analysis set (FAS) comprises all patients who are assigned to receive study treatment as per the ITT principle, regardless of whether or not they subsequently go on to receive study treatment or whether they deviate from the protocol in any major way.

- The modified intent-to-treat (mITT) set comprises all patients who are assigned to receive study treatment and have at least 1 post-baseline efficacy assessment (RECIST 1.1), even if they deviate from the protocol in any major way. The mITT will also include any patient that goes off study treatment because of clinical progression prior to the first scheduled per-protocol scan.

- The safety analysis set comprises all patients who receive any amount of study drug.

- The per-protocol set (PPS) comprises all patients who are assigned to receive study treatment, receive at least 1 injection of study treatment, have at least 1 post-baseline efficacy assessment (RECIST 1.1), and do not deviate from the protocol in any major way.

All efficacy analyses will be based on the FAS and will be conducted on the mITT set and PPS populations for exploratory purposes. For CRC patients, only those with MSS and MSI-L will be included in the efficacy primary analysis. The safety analyses will be based on the safety analysis set and will group patients according to treatment actually received. Secondary and exploratory efficacy analyses will be performed on the ITT/FAS as well as on the mITT and PPS populations for exploratory purposes.

Major protocol deviations will be defined in more detail in the study statistical analysis plan (SAP), and may include, but not be limited to, incorrect diagnosis and poor compliance.

All analyses using the PPS will group patients according to treatment actually received.

7.5.1. Prior Therapies

All prior therapies used in the treatment of any of the tumor types under study will be collected from patients, including drug name, start and stop dates and treatment response. Data will be summarized in tables and presented in the listings. Descriptive statistics will be used to assess the impact of prior treatments on the efficacy endpoints.

7.6. Statistical Analysis Methodology

Data will be summarized and/or analyzed by cohort. Safety and demographic data will be summarized using standard tabulations and listings. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum value, and maximum value. Continuous variables may be summarized by a clinically relevant discretization, as appropriate. Categorical variables will be summarized using frequency counts and percentages. Time-to-event data will be summarized using the Kaplan-Meier method. Where appropriate, 95% confidence intervals around point estimates will be presented, and estimates of the median and other quantiles, as well as individual time points (e.g., 3-month, 6-month, and 12-month rates), will be produced. Data will be provided in data listings.

Details of the statistical analyses, methods, and data conventions are described in the SAP.

7.6.1. Analysis of Primary Efficacy Endpoint

For each tumor-specific cohort, a Bayesian approach with non-informative Jeffreys prior beta distribution with parameters a = 0.5 and b = 0.5 will be used to estimate the ORR and its 95% credible interval based on the posterior distribution.

At the time of analysis, within each tumor-specific cohort, the prior distribution will be updated with all available data to obtain the posterior distribution of the true ORR. The posterior probabilities that ORR exceeds TV and LRV will be reported for each cohort. A high posterior probability that ORR > LRV will support a “Go” decision to continue development in the cohort, and a low posterior probability that ORR > TV will support a “Stop” decision to halt development in the cohort. A “Consider” decision results if neither a Stop nor a Go decision can be made. The specific criteria for making a Stop, Consider, or Go decision within each tumor-specific cohort are derived using the following acceptable risks:

- 10% false stop risk: maximum acceptable probability that ORR > TV given that a Stop decision is made.

- 20% false go risk: maximum acceptable probability that ORR ≤ LRV given that a Go decision is made

Before reaching the planned sample size in a cohort, the posterior probabilities will be updated continuously after each patient or group of patients and will be used to determine, within each cohort, the predictive probability of eventually reaching a Stop decision at the planned sample size. If this predictive probability is ≥ 80%, then enrollment in that cohort may be stopped early for futility. Definitions of the decision boundaries can be found in Section 7.6.6.

In general, Stop/Go and futility decision criteria are non-binding and may be regarded as guidance and information to be integrated with a full medical review of safety and efficacy data observed at the time of analysis in determining the next course of action.

No tests of statistical significance are planned.

Patients with missing ORR will be conservatively classified as non-responders for the primary analysis.

7.6.2. Analysis of Secondary Efficacy Endpoints

Secondary endpoints will be summarized by cohort using descriptive statistics. No formal tests of hypotheses are planned. Duration of response (DOR) and TTR will be evaluated using Kaplan-Meier estimates and curves will be generated based on these estimates.

7.6.3. Analyses of Exploratory Endpoint

Analysis of exploratory endpoints will be defined in the study SAP.

7.6.4. Safety Analyses

All safety analyses will be based on the safety analysis set. Specifically for safety, t-zero for all time measurements assumes the date of first GM-CSF administration (day -2 of the entire protocol schedule).

7.6.4.1. Adverse Events

Missing information regarding AEs will be imputed in a conservative manner. For example, a missing relatedness will be assumed to be certainly related; a missing severity will be assumed to be severe and so on.

All AEs will be coded using the latest version of MedDRA.

The severity of AEs will be coded using CTCAE v5.0.

All TEAEs will be summarized and presented in the listings by the number of patients reporting an event, the percentage of patients with that event, and the grade, duration, and relationship to treatment. Percentages will be based on the number of patients who received each treatment during the study. The incidence of SAEs, including death, and AEs leading to study treatment discontinuation will also be tabulated.

7.6.4.2. Laboratory Test Results

For all laboratory tests with continuous results, absolute value and change from baseline will be summarized by visit and treatment group. For laboratory tests with categorical results, shift from baseline will be summarized by visit and treatment group.

Shift tables for laboratory test results by severity will be produced and, for a subset of tests to be specified in the study SAP, separate shift tables indicating hyper- and hypodirectionality of change will be produced.

Shift tables for urine dipstick test results by grade may also be produced as appropriate.

Clinically significant laboratory test results will be flagged and listed. Reference ranges will be provided.

7.6.4.3. 12-Lead Electrocardiogram Results

Twelve-lead electrocardiogram (ECG) measurements will be recorded at the pretreatment screening visit. Each ECG will be classified as “abnormal” or “normal” and the relevance of the abnormality will be recorded as “clinically significant” or “not clinically significant.”

7.6.4.4. Physical Examination

Physical examinations will be performed at the pretreatment screening visit. Abnormal findings identified will be followed until resolution or stabilization. All ongoing findings will be recorded as pretreatment AEs and will be graded by CTCAE v5.0.

7.6.4.5. Vital Signs

Vital signs (body temperature [centigrade or Fahrenheit], systolic and diastolic blood pressure [BP], heart rate, and respiratory rate) and weight at each visit, plus height and weight at pretreatment screening for calculation of body mass index will be summarized over time in terms of absolute values and changes from baseline by visit and treatment group. For each parameter, a shift table comparing the baseline value to the maximum on-treatment value by treatment group will be presented.

7.6.4.6. Eastern Cooperative Group Performance Status

The ECOG performance status will be measured at each visit. The definition of each ECOG grade is presented in Appendix 12.3 (Oken et al, 1982). The ECOG data will be summarized by treatment group and visit.

7.6.5. Interim Analyses

Not applicable.

7.6.6. Go/No-Go and Futility Monitoring Guidelines

This study uses a Bayesian monitoring approach to guide decision-making using data on the primary efficacy endpoint (ORR) within each cohort. The specific criteria for making a Stop, Consider, or Go decision within each tumor-specific cohort at the planned sample size are derived using the following acceptable risks:

- 10% false stop risk: maximum acceptable probability that ORR > TV given that a Stop decision is made.
- 20% false go risk: maximum acceptable probability that ORR ≤ LRV given that a Go decision is made

The Stop or Go decision criteria in each cohort are presented in Table 14.

Table 14 Decision Criteria for a Stop or Go Decision in Each Cohort at the Planned Sample Size

	Planned Sample Size	Target Value (TV)	Lower Reference Value (LRV)	Minimum Number of Responses for a Go Decision	Maximum Number of Responses for a Stop Decision
CRC	20	20%	10%	4	1
OvC	20	20%	10%	4	1
SCLC	20	40%	30%	8	5
TNBC	15	25%	15%	4	1
AML	15	25%	15%	4	1

AML = acute myeloid leukemia; CRC = colorectal cancer; ORR = overall response rate; OvC = ovarian cancer; LRV = lower reference value; SCLC = small cell lung cancer; TV = target value

Before reaching the planned sample size in a cohort, the posterior probabilities will be updated continuously after each patient or group of patients and will be used to determine, within each cohort, the predictive probability of a Stop decision at the planned sample size. If this predictive probability is ≥ 80%, then enrollment in that cohort may be stopped early for futility. The criteria for early futility stopping within each cohort are as follows:

CRC or OvC (N = number of patients currently enrolled in the cohort):

- If N < 8, there is insufficient data on ORR for a futility recommendation;
- If N ≥ 8, futility stopping considered if no responses observed;
- If N ≥ 18, futility stopping considered if ≤1 response observed.

SCLC (N = number of patients currently enrolled in the cohort):

- If N < 3, there is insufficient data on ORR for a futility recommendation;
- If N ≥ 3, futility stopping considered if no responses observed;
- If N ≥ 7, futility stopping considered if ≤1 response observed;
- If N ≥ 11, futility stopping considered if ≤2 responses observed;
- If N ≥ 14, futility stopping considered if ≤3 responses observed
- If N ≥ 17, futility stopping considered if ≤4 responses observed

TNBC or AML:

- If N < 6, there is insufficient data on ORR for a futility recommendation;
- If N ≥ 6, futility stopping considered if no responses observed;
- If N ≥ 13: futility stopping considered if ≤1 response observed.

After reaching the planned sample size in a cohort, enrollment may be increased by approximately 10 additional patients in that cohort if the sponsor determines that further data on the primary or secondary endpoints is needed to clarify the efficacy signals for a Go/No-Go decision. In case additional patients are enrolled in a cohort, the decision boundaries for the expanded cohorts will be calculated using the same levels of acceptable risks used to

derive the initial boundaries, and futility monitoring will continue as before using ≥ 80% predictive probability of a Stop decision as a threshold to recommend early futility stopping.

In general, Stop/Go and futility decision criteria are non-binding and may be regarded as guidance and information to be integrated with a full medical review of safety and efficacy data observed at the time of analysis in determining the next course of action.

7.7. Data Quality Assurance

Data entered on the eCRFs must be verifiable against the existing medical records at the investigational site. Data captured on the eCRFs will be reviewed by a SELLAS clinical monitor or designee against the existing medical records at the investigational site for validity and completeness according to procedures outlined in the monitoring plan. After completion of monitoring of the eCRFs, the eCRFs will be reviewed by SELLAS or its designee for data management and analysis purposes. If necessary, the investigational site will be periodically contacted for corrections and/or clarifications of the data.

7.7.1. Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients participating in this study. Data will be collected for all patients signing consent. The investigator agrees to maintain accurate source documentation as part of the case histories. Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, and patient-reported assessments, as well as the results of diagnostic tests such as laboratory tests and ECGs.

Investigative site personnel will enter patient data into eCRFs. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. All data entered into the eCRF must be substantiated by a source document. Accurate completion of the eCRFs for all patients is the responsibility of the investigator. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

SELLAS Life Sciences Group (SELLAS) or its designee will designate the EDC system to be used. The eCRFs must be kept current to reflect patient status at each phase during the course of the study. Patients are not to be identified on eCRFs by name; appropriate coded identification and patient initials must be used. The investigator must keep a separate log of patient names and addresses. This log is subject to regulatory authority inspection. Because of the potential for errors and inaccuracies in recording data onto eCRFs, originals of laboratory and other test results must be kept on file with the patient's clinical chart. These test results must be available at all times for inspection by the regulatory authority, the sponsor, and the sponsor representatives such as CRO monitors.

An eCRF must be completed for each patient enrolled in the study, including those removed from the study for any reason. The reason for removal must be noted by the investigator for each patient.

SELLAS Life Sciences Group or its designee will review all eCRFs for completeness. The investigator will be contacted for corrections and/or clarifications. Intensive efforts will be made to minimize missing data. Those patients with missing data regarding OS will be censored at that time. Missing data on secondary endpoints will be addressed using imputation methods that reduce the risk for bias.

Clinical data management will be performed in accordance with applicable SELLAS policies and data cleaning procedures to ensure the integrity of the data, (e.g., removing errors and inconsistencies in the data). Adverse events and concomitant medication terms will be coded using the latest version of MedDRA, an internal validated medication dictionary.

After database lock, each study site will receive a CD-ROM containing all of their site-specific eCRF data as entered into the electronic data capture system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site’s data from the study will be created and sent to the sponsor for storage. The CRO will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

8. Ethics

8.1. Independent Ethics Committee or Institutional Review Board

Federal regulations (United States 21 CFR Part 56.103) and the ICH guidelines require that approval be obtained from an IRB before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee. Copies of all IRB correspondence with the investigator should be provided to SELLAS.

All IRB/IEC approvals should be signed by the IRB chairperson or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. SELLAS Life Sciences Group is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. Adverse events must be reported to the IRB as required. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients. The IRB will receive notification of the completion of the study and final report within 3 months of study completion or termination.

8.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, relevant SELLAS policies and procedures, and all applicable regulations.

8.3. Patient Information and Consent

In accordance with guidelines in the Federal Register, Volume 48, Number 17, 1982, pages 8951-8952, a written informed consent shall be obtained from each patient before entering the study or performing any study procedure. This Phase 2 study involves research that presents risk, but holds the possibility of direct benefit to the individual patient (46.405-45 CFR part 46).

An informed consent form (ICF) template will be provided by SELLAS or its designee to investigative sites. If any institution-specific modifications to the informed consent are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the site investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF. The site investigator shall retain the original signed consent form(s) with the study center’s records. Each patient/legal guardian will also be given a copy of his or her signed consent form(s).

9. Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not necessarily result in protocol amendments.

9.1. Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study treatment may ultimately be marketed, but the patient's name will not be disclosed in these documents. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information. All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the governing regulatory authority(ies), or the IRB. The patient's name may be disclosed to the sponsor of the study, SELLAS, or the governing health authorities if they inspect the study records.

Written authorization is to be obtained from each patient and/or the patient's legally authorized representative in accordance with the applicable privacy requirements (i.e., the HIPAA Standards for Privacy of Individually Identifiable Health Information).

In accordance with HIPAA requirements, additional purposes of this study include the following:

- To publish anonymous patient data from the study; and
- To create and maintain a data repository.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor (SELLAS) nor CRO (Cancer Insight, LLC) is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor CRO is financially responsible for further treatment of the patient's disease.

9.3. Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study

- IRB -approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian

9.4. Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

9.5. Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.6. Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB as appropriate.

In accordance with the regulation 21 CFR 312.32, the sponsor shall within 60 days of the anniversary date that the investigational new drug application went into effect to submit a brief report of the progress of the investigation.

9.7. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8. Records Retention

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The following documents will be maintained for 2 years beyond product FDA and European Union full approval of the combination of galinpepimut-S plus pembrolizumab (if such is granted in the future based on the results of this study or other studies) or until SELLAS notifies the site in writing with permission to either send the documents to another location or locally destroy these documents:

- eCRFs - a copy of each patient's full eCRF must be kept.
- Patient files/signed informed consent - which substantiates the data entered on the eCRFs for all required test and evaluation procedures and verifies that the patient has signed an informed consent to enter the study.
- Patient exclusion record - which should reflect the reason any patient was screened and found ineligible for the study.
- Monitoring log - listing dates of monitor visits.
- Regulatory documents - including protocol and all versions, investigator brochure and all versions, FDA Form 1572, curricula vitae, IRB correspondence, IRB

approval/renewals and IRB approved consent form, copy of all investigators and subinvestigator curricula vitae, financial disclosure forms each year filed with their IRB of record, current medical license during duration of the study, and other documents as requested by SELLAS or any regulatory agency.

- AE eCRF - which should explain any serious or unexpected adverse experiences. This also includes all SAE reports, MedWatch forms, and/or Council for International Organizations of Medical Sciences forms. All correspondence with the site's IRB/IEC of record, regulatory authority(ies), and SELLAS.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

SELLAS Life Sciences Group requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

9.9. Publications

SELLAS Life Sciences Group, as the Sponsor, has proprietary interest in this study. Data are the property of the Sponsor and cannot be published without prior authorization from the sponsor. After completion of the study, the data may be considered for reporting at a scientific meeting and/or for publication in a scientific journal. Authorship and manuscript composition of any publication will reflect joint cooperation between multiple investigators and sites and SELLAS personnel. SELLAS will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Authorship will be established by site enrollment. The first author will be from the highest enrolling site. The last author will be from the site that contributes the most to the development of the protocol, data analysis, and drafting of the article for publication. The sponsor has final approval authority over all such issues. No individual publications will be allowed before completion of the final report of the multicenter study except as agreed by SELLAS, but data and publication thereof will not be unduly withheld.

10. Study Management and Monitoring**10.1. External Data Monitoring Committee**

Not applicable.

10.2. Monitoring of the Study

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Prior to initiation of the study, SELLAS or its designee will visit the study site to review with the site personnel information about the study treatment, protocol, and other regulatory document requirements, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs including SAEs.

During the study, a monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will assess the site for compliance with regulatory documentation and will focus on accurate and complete recording of data on eCRFs from source documents, adherence to protocol and GCP, SAE reporting, and drug accountability records. At all times, study-related correspondence, patient records, original signed consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and electronic copies of eCRFs, if applicable, should be maintained on file.

The investigator must agree to allow the monitor access to the clinical supplies, dispensing, and storage areas and to all relevant clinical files of the study patients. Key study personnel must be available to assist the monitor during the visits. In addition, the investigator should make every effort to be available for 30 to 60 minutes at the time of the clinical monitoring check-out meeting at the end of each day of the monitoring visit to discuss findings and needed assistance to complete the monitoring visit successfully.

10.2.1. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA or other regulatory agency) access to all study records.

The investigator should promptly notify SELLAS and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.3. Management of Protocol Amendments and Deviations

10.3.1. Modification of the Protocol

Each site investigator must not implement any deviation from or changes to the protocol without approval by SELLAS and prior review and documented approval/favorable opinion from the IRB, except where necessary to eliminate immediate hazards to study patients or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers). Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before patients can be enrolled into an amended protocol. The site investigator will report to the IRB and SELLAS and SELLAS will report to the regulatory authority any changes in the research protocol and all unanticipated problems involving risks to human patients and others, and no changes will be made in the research activity without IRB approval. SELLAS will report to the regulatory authority any changes in the research protocol.

10.3.2. Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to regulatory authority regulations or ICH GCP guidelines and will lead to the patient being withdrawn from the study (Section 4.2).

There should be no deviations or departures from the protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB approval. If an emergency occurs that requires departure from this protocol, the investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the medical monitor. Such contacts will be made to permit a decision as to whether or not the patient will be continued on the study. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement (if not already done), and to the regulatory authorities, if required.

The site investigator or designee must clearly document and explain in the patient's source documentation any deviation from the approved protocol. Protocol deviations will also be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The sponsor and IRB should be notified of all protocol deviations in a timely manner.

10.4. Study Termination

Although SELLAS has every intention of completing the study, the sponsor reserves the right to close an investigational site or terminate the study at any time for clinical or administrative

reasons. In addition, the study may be stopped at a site at any time by the site investigator with appropriate notification.

10.5. First Interpretable Results (FIR) Report

A first interpretable results (FIR) report will be prepared. The exact data to be included in the FIR and its structure will be determined by the study master co-Principal Investigators, the data management/analysis and biostatistical teams (designees of SELLAS), the medical monitor(s), and the Chief Medical Officer and Head of Clinical Development of SELLAS

10.6. Final Complete Clinical Study Report (CSR)

Whether the study is completed or prematurely terminated, the investigator, where applicable, should inform the institution. The investigator/institution should provide the IRB with a summary of the study's outcome.

SELLAS Life Sciences Group will ensure that both interim, as well as final complete clinical study reports are prepared (as applicable) and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

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12. Appendices

12.1 Appendix 1. Azacitidine (Vidaza®) US Prescribing Information

https://media.celgene.com/content/uploads/vidaza-pi.pdf (Celgene Corporation, Summit, NJ, USA, Sep, 2018)

12.2. Appendix 2. Decitabine (Dacogen®) US Prescribing Information

https://www.otsuka-us.com/media/static/dacogen-pi.pdf (Otsuka America Pharmaceutical, Inc., Rockville, MD, Dec. 2018)

12.3. Appendix 3. WT1 IHC Assessment and Documentation Form

CLINICAL STUDY PROTOCOL SLS17-201/ MK3475-770

A PHASE 1/2 STUDY OF GALINPEPIMUT-S IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH SELECTED ADVANCED CANCERS

WT1 IHC Assessment and Documentation Form

Assessment of Tumor Positivity for Expression of WT1 in Biopsy Material by WT1 Immunohistochemistry (IHC)

Per Section 4.1.1. (Subject Inclusion Criteria), subheading 4 (b). of of the protocol:

Patients' metastatic disease deposits (for patients with solid tumors)/bone marrow leukemic cell deposits (for patients with AML) will be evaluated for WT1 protein expression, as detectable by IHC analysis of banked (paraffin-embedded) or freshly biopsied tumor material.

- IHC evidence of WT1 expression will be performed according to the technique described by Dupont et al. (Gynecol Oncol. 2004;94:449-55).
- Expression will be graded according to an adaptation of the German Immunoreactive Score (IRS) (Remmele W & Stegner H-E. Dtsch Ärztbl. 1986;83:3362-4; *Idem*. Pathologe. 1987;8:138-40).
- Only WT1 tumors with moderate to strong immunoreactive scores (4-12) will be considered positive.

The German IRS Scale for WT1 assessment by IHC is shown below:

Percentage of positive cells	**X Intensity of Staining**	**= IRS (0 – 12) (multiplication product)**
0 = no positive cells	0 = no color reaction	0 – 1 = negative
1 = < 10% of positive cells	1 = mild reaction	2 – 3 = mild
2 = 10-50% positive cells	2 = moderate reaction	4 – 8 = moderate
3 = 51-80% positive cells	3 = intense reaction	9 – 12 = strongly positive
4 = > 80% positive cells		

IRS – points	**IRS – classification**

0 – 1	0 = negative
2 – 3	1 = positive, weak expression
4 – 8	**2 = positive, moderate expression**
9 – 12	**3 = positive, strong expression**

The data on patient's tumor/leukemic BM deposits WT1 expression levels will be collected using the Table below:

Patient Initials	**Patient Study ID**	**WT1 Immunoreactive Score (IRS)**	**Date of Score Confirmation**
Source of Tested Slides:			
Institution	Date of Accession	Accession Number	Section/Specimen Type

_____ _____

Pathologist's Name and Signature Date

12.4. Appendix 4. Eastern Cooperative Group Performance Status

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

12.5. Appendix 5. Revised Recommendations of The International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia

Response Criteria in AML

Response Criterion	Time of Assessment	Neutrophils (μ/L)	Platelets (μ/L)	Bone Marrow Blasts (%)	Other
Early treatment assessment	7-10 days after therapy	NA	NA	< 5	
Morphologic leukemia-free state	Varies by protocol	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	Varies by protocol	>1,000	> 100,000	< 5	Transfusion EMD
Cytogenetic CR	Varies by protocol	>1,000	> 100,000	< 5	Cytogenics-normal, EMD
Molecular CR	Varies by protocol	>1,000	> 100,000	< 5	Molecular-negative, EMD
Partial remission (PR)	Varies by protocol	> 1,000	> 100,000	> 50% decrease vs baseline or decrease to 5-25%	Blasts < 5% if Auer rod positive (FAB M2 & M3 subtypes only)

Abbreviations: AML, acute myelogenous leukemia; EMD, extramedullary disease; CR, complete remission.

From: Cheson BD, Bennett, JM, Kopecky, KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003;21(24):4642-49.

12.6. Appendix 6. Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management (see Table 10 and Figure 14 in earlier sections of this document). This decision by the site investigator should be based on the patient's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by

iRECIST, per Investigator assessment. Images should continue to be archived for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND

- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

NOTE: If a patient has confirmed radiographic progression (iCPD) as defined above, but the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the sponsor. In this case, if study treatment is

continued, tumor imaging should continue to be performed following the intervals as outlined below.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour et al, 2017).