Clinical Trial Protocol
NLG0304

A Phase 2b Study of Immune Checkpoint Inhibition With or Without Dorgenmeltucel-L (HyperAcute Melanoma) Immunotherapy for Stage IV Melanoma Patients

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Investigational Agent:
Dorgenmeltucel-L (HyperAcute Melanoma) Immunotherapy (HAM)

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Principal Investigators and Participating Sites

Multiple institutions throughout the United States will be conducting this study. For a full list of participating institutions please refer to the Clinicaltrials.gov website listing for this study (NCT02054520).

NON-TECHNICAL ABSTRACT:

Unfortunately, despite the best clinical efforts and breakthroughs in biotechnology, most patients diagnosed with advanced Stage melanoma continue to die from their disease. Reasons for this include: 1) patients are often diagnosed at a time when their melanoma has already spread to other sites such as the chest cavity, bone, liver, and brain limiting the options for surgical excision and 2) the cancer cells are resistant or become resistant to chemotherapy drugs used to treat the patient. Resistance to one type of chemotherapy agent often rapidly leads to resistance against many other chemotherapy drugs.

Harnessing the human immune system to target cancer could result in the development of effective treatment options against cancer and potentially enhance the effect of cytotoxic chemotherapy. Cancer cells produce a number of abnormal proteins or abnormal amounts of certain proteins found in normal cells. In some cancers, the abnormal protein expression may lead to an immune response against the cancer cells much in the same way the immune system responds to an infection. In progressive cancer however, the immune system fails to identify or respond to these abnormalities, and the cancer cells are not attacked or destroyed for reasons not yet fully understood.

From a practical standpoint, a successful tumor immunotherapy will likely require a combination treatment with additional therapeutic interventions that both activate an immune response and remove redundant mechanisms of tolerance maintenance. This clinical trial utilizes a combination of the two methods of cancer immunotherapy: the first, dorgenmeltucel-L, is intended to educate the human immune system to recognize the abnormal components found in melanoma cells, resulting in an immune response intended to destroy or block the growth of the cancer; and the second, a checkpoint inhibitor, will overcome tumor-induced immune suppression.

The investigational immunotherapy, dorgenmeltucel-L, helps the immune system of melanoma patients “identify” and target the cancerous tissue. This immunotherapy is engineered to mimic a key difference between human cells and the cells of other mammals. When a human immune system identifies cells or tissue labeled as “foreign” in this way, it “rejects” these cells or tissue. This “rejection” occurs when the patient’s immune system responds to differences between the cells of the transplanted organ and their own immune system by attacking the foreign tissue in the same way as it would attack infected tissue. This form of rejection is very rapid and highly destructive and the immunity it generates is long-lasting. This is called hyperacute rejection, and the immunotherapy used in this protocol tries to harness this response to teach a patient’s immune system to fight their melanoma just as the body would learn to reject a transplanted organ from an animal.

To achieve this hyperacute response, a mouse gene is placed into cultured human melanoma cells. These cells will express a molecule that will stimulate a strong immune response in humans. These cancer cells are irradiated to prevent any growth and then injected, along with the additional therapies, into patients with melanoma. The presence of the molecule will stimulate the patient’s immune system to kill the injected immunotherapy cells. As part of the process of destroying the immunotherapy cells, the patient’s immune system is stimulated to identify many differences between these cancer cells and normal human cells. This extra stimulation is thought to encourage immune responses against the melanoma in the patient based on shared abnormalities of the melanoma immunotherapy cells and the patient’s melanoma cells.

The standard of care agents used in this study, the checkpoint inhibitors of ipilimumab, nivolumab, or pembrolizumab, target mechanisms by which tumors evade a patient's immune system. Tumors acquire numerous potentially immune response provoking mutations as they develop. The immune system plays an important surveillance role in detecting and eliminating these malignant cells as they arise. This means that in order to grow, tumors must evade the host immune response. In essence, the host immune system must be rendered functionally tolerant to tumor-associated antigens. A phenomenon as complex as systemic tolerance requires that the tumor enlists the natural array of host regulatory pathways that already exist in the immune system.

In this protocol, patients with advanced melanoma will be given a checkpoint inhibitor (either ipilimumab, nivolumab, or pembrolizumab) with or without the dorgenmeltucel-L immunotherapy to assess the safety and progression-free survival (PFS) and overall survival (OS) rates in this patient population.

PROTOCOL SYNOPSIS:

Title:	A Phase 2b Study of Immune Checkpoint Inhibition With or Without Dorgenmeltucel-L (HyperAcute Melanoma) Immunotherapy for Patients with Stage IV Melanoma
Primary Objectives:	*Safety*: To determine the safety of administration of immune checkpoint inhibition with or without dorgenmeltucel-L (HyperAcute Melanoma (HAM)) immunotherapy for patients with Stage IV melanoma. *Efficacy*: To assess the progression-free survival (PFS) of metastatic melanoma patients treated with immune checkpoint inhibition with or without dorgenmeltucel-L immunotherapy.
Secondary Objective:	*Efficacy*: To assess the overall response rate, duration of response, duration of stable disease, and overall survival (OS) of patients with Stage IV melanoma treated with immune checkpoint inhibition with or without dorgenmeltucel-L immunotherapy. *Biologic activity*: To measure possible anti-tumor immune responses in melanoma metastases in patients. To further determine whether the humoral and cellular mediated arms of the host immune system are activated secondary to dorgenmeltucel-L combined with immune checkpoint inhibition. Lastly, to perform correlative studies of patient blood samples (and tumor when available) to determine the mechanism of any observed anti-tumor effect.
Population:	Patients with Stage IV metastatic melanoma **Arm 1**: Patients will receive immune checkpoint inhibition plus dorgenmeltucel-L Immune checkpoint inhibition consists of the treating physician's standard of care choice of ipilimumab, nivolumab, or pembrolizumab. **Arm 2**: Patients will receive immune checkpoint inhibition alone Immune checkpoint inhibition consists of treating physician's standard of care choice of ipilimumab, nivolumab, or pembrolizumab.
Sample Size:	One hundred total patients will be randomized with equal allocation to Arm 1 (50 patients) and Arm 2 (50 patients). Patients will be stratified by immune checkpoint therapy and disease status and categorized as follows: 1) Immune checkpoint inhibition 2) Patients with unresectable advanced disease 3) Patients with resectable advanced disease who receive the immunotherapy in advance of resection

4) Patients with resected isolated advanced disease who are treated in a no apparent disease (NAD) state

Investigational Drugs: Dorgenmeltucel-L (HyperAcute Melanoma) immunotherapy consisting of equal cell doses of each of three allogeneic melanoma cancer cell lines engineered to express the murine α(1,3)galactosyltransferase gene.

Dosage Treatment:

Arm 1 will receive either:
Arm 1A - ipilimumab at 3 mg/kg given every 3 weeks x 4 doses **or**
Arm 1B - nivolumab at 240 mg given every 2 weeks **or**
Arm 1C - pembrolizumab at 2 mg/kg given every 3 weeks **AND**
300 Million HAM cells per each immunization, given every week x 4, every 2 weeks for 5 months, every month for 6 months, and every 3 months x 4;

Arm 2 will receive either:
Arm 2A - ipilimumab at 3 mg/kg given every 3 weeks x 4 **or**
Arm 2B - nivolumab at 240 mg given every 2 weeks **or**
Arm 2C - pembrolizumab at 2 mg/kg given every 3 weeks

Clinical Endpoints:

1. Safety
2. Progression-free survival (PFS)
3. Overall response rate
4. Duration of objective response
5. Duration of stable disease
6. Overall survival (OS)
7. [redacted]

Protocol Schemas for Arm 1A and Arm 2A
Ipilimumab plus dorgenmeltucel-L - Arm 1A
Ipilimumab Alone – Arm 2A

Arm 1A: HAM + IPILIMUMAB

Month	Week	Day	Treatment
	1	1	HAM
	2	8	HAM
	3	15	HAM
1	4	22	HAM + IPI
	5	29	REST
	6	36	HAM
	7	43	IPI
2	8	50	HAM
	9	57	REST
	10	64	HAM + IPI
	11	71	REST
3	12	78	HAM
	13	85	IPI
	14	92	HAM
	Evaluate for Response		
	15	99	REST
4	16	106	HAM
	17	113	REST
	18	120	HAM
	19	127	REST
5	20	134	HAM
	21	141	REST
	22	148	HAM
	23	155	REST
6	24		HAM
	Evaluate for Response		
7			HAM
8			HAM
9			HAM
	Evaluate for Response		
10			HAM
11			HAM
12			HAM
	Evaluate for Response		
15			HAM
	Evaluate for Response		
18			HAM
	Evaluate for Response		
21			HAM
	Evaluate for Response		
24			HAM
	Evaluate for Response		

Arm 2A: IPILIMUMAB ALONE

Week	Day	Treatment
1	1	IPI
2	8	REST
3	15	REST
4	22	IPI
5	29	REST
6	36	REST
7	43	IPI
8	50	REST
9	57	REST
10	64	IPI
11	71	REST
12	78	REST
Evaluate for Response		

IPI Alone Group: After treatment, observe for disease progression. If disease progresses, subjects go off study but will continue to be followed for survival status.

Protocol Schemas for Arm 1B and Arm 2B
Nivolumab plus dorgenmeltucel-L - Arm 1B
Nivolumab Alone – Arm 2B

Arm 1B: HAM + NIVOLUMAB

Month	Week	Day	Treatment
	1	1	HAM
	2	8	HAM
	3	15	HAM
1	4	22	HAM + NIVO
	5	29	REST
	6	36	HAM + NIVO
	7	43	REST
2	8	50	HAM + NIVO
	9	57	REST
	10	64	HAM + NIVO
	11	71	REST
3	12	78	HAM + NIVO
	13	85	REST
	14	92	HAM + NIVO
	Evaluate for Response		
	15	99	REST
4	16	106	HAM + NIVO
	17	113	REST
	18	120	HAM + NIVO
	19	127	REST
5	20	134	HAM + NIVO
	21	141	REST
	22	148	HAM + NIVO
	23	155	REST
6	24		HAM + NIVO
	Evaluate for Response		
	Continue Nivolumab Q2 weeks		
7			HAM
8			HAM
9			HAM
	Evaluate for Response		
10			HAM
11			HAM
12			HAM
	Evaluate for Response		
15			HAM
	Evaluate for Response		
18			HAM
	Evaluate for Response		
21			HAM
	Evaluate for Response		
24			HAM
	Evaluate for Response		

Arm 2B: NIVOLUMAB ALONE

Week	Day	Treatment
1	1	NIVO
2	8	REST
3	15	NIVO
4	22	REST
5	29	NIVO
6	36	REST
7	43	NIVO
8	50	REST
9	57	NIVO
10	64	REST
11	71	NIVO
12	78	REST
Evaluate for Response		

Nivolumab Alone Group: Continue treatment Q2 weeks until disease progression or significant toxicity. Evaluate disease every 3 months. If disease progresses, subjects go off study but will continue to be followed for survival status.

Protocol Schemas for Arm 1C and Arm 2C
Pembrolizumab plus dorgenmeltucel-L - Arm 1C
Pembrolizumab Alone – Arm 2C

Arm 1C: HAM + PEMBROLIZUMAB

Month	Week	Day	Treatment
	1	1	HAM
	2	8	HAM
	3	15	HAM
1	4	22	HAM + Pembro
	5	29	REST
	6	36	HAM
	7	43	Pembro
2	8	50	HAM
	9	57	REST
	10	64	HAM + Pembro
	11	71	REST
3	12	78	HAM
	13	85	Pembro
	14	92	HAM
	Evaluate for Response		
	15	99	REST
4	16	106	HAM + Pembro
	17	113	REST
	18	120	HAM
	19	127	Pembro
5	20	134	HAM
	21	141	REST
	22	148	HAM + Pembro
	23	155	REST
6	24		HAM
	Evaluate for Response		
Continue Pembrolizumab Q3 weeks			
7			HAM
8			HAM
9			HAM
	Evaluate for Response		
10			HAM
11			HAM
12			HAM
	Evaluate for Response		
15			HAM
	Evaluate for Response		
18			HAM
	Evaluate for Response		
21			HAM
	Evaluate for Response		
24			HAM
	Evaluate for Response		

Arm 2C: PEMBROLIZUMAB ALONE

Week	Day	Treatment
1	1	Pembro
2	8	REST
3	15	REST
4	22	Pembro
5	29	REST
6	36	REST
7	43	Pembro
8	50	REST
9	57	REST
10	64	Pembro
11	71	REST
12	78	REST
Evaluate for Response		

Pembrolizumab Alone Group: Continue treatment until disease progression or significant toxicity. Evaluate disease every 3 months. If disease progresses, subjects go off study but will continue to be followed for survival status.

Table of Contents

PRECIS

According to statistics of the American Cancer Society, an estimated 73,800 individuals will be diagnosed with melanoma and 9,900 will die of the disease in 2015 in the Unites States despite current therapy. This protocol attempts to exploit an approach to melanoma immunotherapy using a naturally occurring barrier to xenotransplantation in humans to increase the effectiveness of immunizing patients against their melanoma. The expression of the murine α(1,3)galactosyltransferase [α(1,3)GT] gene results in the cell surface expression of α(1,3)galactosyl-epitopes (αgal) on membrane glycoproteins and glycolipids. These epitopes are the major target of the hyperacute rejection response that occurs when organs are transplanted from non-primate donor species into man. Human hosts often have pre-existing anti-α-gal antibodies that bind α-gal epitopes and lead to rapid activation of complement and cell lysis. The pre-existing anti-α-gal antibodies found in most individuals are thought to be due to exposure to α-gal epitopes that are naturally expressed on normal gut flora leading to chronic immunological stimulation. These antibodies may comprise up to 1% of serum IgG.

In this phase 2b study, patients with advanced Stage melanoma will receive immune checkpoint inhibition consisting of ipilimumab, nivolumab, or pembrolizumab per the treating physician's standard of care. In addition to the immune checkpoint therapy, half of the patients will also receive dorgenmeltucel-L. Dorgenmeltucel-L is composed of irradiated allogeneic melanoma cell lines (HAM-1, HAM-2 and HAM-3). These cell lines have been transduced with a recombinant Moloney murine leukemia virus (MoMLV)-based retroviral vector expressing the murine α(1,3)GT gene. Endpoints of the study include safety assessments, efficacy, and immunological responses.

1 INTRODUCTION

1.1 Objectives

1.1.1 Primary Objective:

To assess safety of an anti-tumor treatment using immune checkpoint inhibition consisting of ipilimumab, nivolumab, or pembrolizumab alone compared to immune checkpoint inhibition plus dorgenmeltucel-L immunotherapy in Stage IV melanoma patients and to assess efficacy as indicated by progression-free survival of those patients treated with immune checkpoint inhibition with or without dorgenmeltucel-L immunotherapy.

1.1.2 Secondary Objectives:

To assess the overall response rate, duration of response, duration of stable disease, and overall survival (OS) of patients with Stage IV melanoma treated with immune checkpoint inhibition with or without dorgenmeltucel-L immunotherapy.

To assess the immunological response of patients with metastatic melanoma undergoing anti-tumor treatment using immune checkpoint inhibition with or without dorgenmeltucel-L immunotherapy in Stage IV melanoma patients.

2 BACKGROUND

2.1 α(1,3)Galactosyltransferase gene therapy and the hyperacute rejection response.

Hyperacute rejection of non-human xenografts

Strong pre-existing immunological barriers to xenotransplantation of solid organs from lower mammals into humans can destroy a transplanted organ within minutes to hours, a phenomenon termed hyperacute rejection.[1] It has been demonstrated that the major cause of hyperacute rejection induced with porcine xenografts transplanted into baboons is secondary to expression of the enzyme α(1,3)galactosyltransferase [α(1,3)GT] and the resulting presentation of αgal residues on the transplanted pig organs.[1,2] α(1,3)GT is expressed in all mammalian species including the mouse (*Mus musculus*), but it is not present in old world primates, apes or humans.[3] The α(1,3)GT gene is not active in humans due to the presence of two base pair frame shift mutations resulting a non-functional pseudogene.[4] Alpha(1,3)GT normally catalyzes the transfer of galactose from uridine-diphosphate galactose (UDP-Gal) to the N-acetyl-lactosamine acceptors on carbohydrate side chains in a specific α(1,3)linkage on a large number of glycoproteins or glycolipids (Galβ1→4GlcNAc-R).

Galβ1→4GlcNAc-R + UDP-Gal→Galα1→3Galα1→4GlcNAc-R

Anti-αgal antibodies present in human sera can recognize this epitope.[3] In fact, pre-existing human antibody against αgal represents almost 1% of total human antibody. These αgal epitopes are the targets for complement-mediated hyperacute rejection.[5] Our strategy will attempt to use

murine α(1,3)GT as a therapeutic transgene in combination with an allogeneic cellular immunotherapy to induce hyperacute rejection of human melanoma.

Other potentially important effects on the immune system

Previous studies have established that multiple membrane glycoproteins on pig cells present αgal residues and are targets for human anti-αgal antibody binding [6]. In addition, many glycoproteins possess multiple carbohydrate side chains and can express multiple different αgal epitopes. Since both opsonization and complement fixation are dependent on epitope density, α(1,3)GT immunogene therapy offers potential advantages over other candidate transgenes. The α(1,3)GT gene expression could permit a large number of membrane glycoproteins to be induced to express these epitopes simultaneously. Opsonization of tumor cells can occur by pre-existing or induced anti-αgal antibodies and should significantly enhance tumor antigen presentation to macrophages by αgal-antibody complex binding to their Fc-receptors. Studies demonstrated that the uptake of human tumor cells into macrophages are significantly enhanced by cell membrane modifications with enzymes using a recombinant, truncated form of an α(1,3)GT.[7] These results using enzymatic modifications of human cell membranes should be transferable to our gene transfer approach. Previous attempts of immunotherapy have employed single cytokine molecules (e.g., IL-2, IL-12, GM-CSF) or single rejection antigens (e.g., HLA B7, melanoma specific tumor antigens) while the α(1,3)GT approach offers the possibility of a broad xenogenization of normal antigens found on tumors.

In humans, implanted murine retroviral vector producer cells (VPC's) are another type of αgal-positive xenograft

VPC's have been used for *in vivo* gene delivery as a potential improvement over direct administration of vector alone to increase transduction efficiency in both animal models and human clinical trials.[8-10] It has been demonstrated that murine retroviral VPC's and the viral vectors they produce both express αgal-residues and therefore are efficiently lysed by antibody and complement within 30 minutes after being exposed to human serum. This is due to the expression of αgal-residues on the cells and the viral envelope derived from the VPC membrane.[11] Link and coworkers demonstrated that heparin, enoxaparin, or sCR1 (soluble form of Complement receptor 1) can specifically block lysis of murine cells by human serum.[12] These workers hypothesized that this disadvantage for murine VPC's could be an advantageous novel method to destroy tumor cells. The hypothesis is that expression of the α(1,3)GT gene using a retroviral vector in allogeneic melanoma cancer cells will lead to αgal epitope expression and anti-αgal antibodies that are known to be present and in high titer in the majority of patients should then bind this epitope and activate the classical and alternative pathway of complement to induce tumor cell lysis possibly enhancing tumor immunogenicity.

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2.2 Pre-Clinical Experience of Dorgenmeltucel-L

All of the components of dorgenmeltucel-L immunotherapy have been evaluated in a variety of preclinical studies in mice as well as in phase 1 and 2 human clinical studies. The safety of dorgenmeltucel-L has been demonstrated *in vivo* in mice. Substantial preclinical data on the safety and efficacy of related immunotherapies have been published. Specific preclinical information is available in the Investigator's Brochure.

2.3 Clinical Experience of Dorgenmeltucel-L (HyperAcute Melanoma)

In the phase 1 dorgenmeltucel-L Trial NLG0104, 6 subjects received the melanoma immunotherapy. Six patients, 2 men and 4 women, mean age- 60 years (range, 36-76), were vaccinated with one priming dose of 500 million cells and up to eleven booster doses of

300 million cells. Observed events unrelated or unlikely to be related to the immunotherapy included Grade 1 fatigue, pruritus, nausea, vomiting, constipation, dysphagia, dermal change, facial edema, hyperglycemia, pain, and nocturia. Grade 1 events possibly related to the immunotherapy included fatigue, nausea, and dysgeusia. Grade 2 events unrelated or unlikely related to the immunotherapy include pruritus, cellulitis, left hemianopsia, and headache. One Grade 3 cellulitis was observed after a brown recluse spider bite in one of the subjects. Events probably or definitely related to the immunotherapy include Grade 1 and 2 injection site reactions to include redness, swelling, and itching. Five of the six patients went off study, 3 due to progression of disease and 2 due to concurrent illness. One subject remains on long-term follow-up with stable disease (> 5 years).

Riker *et al*. have since completed a phase 2 clinical trial of dorgenmeltucel-L (NLG12036, NewLink Genetics) combined with pegylated interferon (Sylatron™, Merck). Trial design consisted of a 12-week regimen with the initial 4 weekly treatments consisting of dorgenmeltucel-L alone (intradermally) followed by 8 additional treatments of dorgenmeltucel-L plus Sylatron™ (subcutaneously, 6 μg/kg). Trial endpoints include clinical response, overall safety and correlative findings for observed anti-tumor effect. They report a total of 25 patients accrued with a median age 60, 68% male with 21 patients completing the trial, 4 stopped due to progressive disease (PD).

By RECIST criteria, of 16 Stage IV patients, there were 2 complete responders (CR), 1 with stable disease (SD) and 4 with no evidence of disease (NED) after resection. For Stage III patients, 4/9 remains NED, 1 patient with slowly progressive disease with a single site resected and currently NED. The median overall survival is 29 months, with 60% of the patients surviving for >1 year and 12/25 (48%) still alive. All evaluable patients (21/21) seroconverted, developing autoimmune antibodies. Vitiligo developed in 4/25 patients, correlating with 2 CR and 2 NED.

They conclude that combinatorial immunotherapy with dorgenmeltucel-L plus Sylatron™ shows clinical efficacy with tumor regression and concomitant immune activation. Optimization of dosing schedules and therapeutic efficacy should be further explored in order to enhance the benefit of this promising immunotherapeutic approach (Riker et al., The Ochsner Journal, 14 (2) 2014:164-174).

2.4 Ipilimumab (anti-CTLA-4 antibody)

Ipilimumab is a monoclonal antibody that blocks the immunosuppressive receptor CTLA-4 on T cells, thus enhancing (disinhibiting) immune responses against the tumor. Because of the role CTLA-4 plays in undermining antitumor T cell responses, the use of CTLA-4 blockade in combination with a range of cancer immunotherapies has been investigated in preclinical models and found to enhance antitumor T cell responsiveness. Ipilimumab has recently been approved by the FDA for unresectable and metastatic melanoma, and has demonstrated preliminary anti-tumor effect as a single agent in other solid tumors, including metastatic NSCLC and prostate carcinoma.

Treatment with ipilimumab increases median overall survival in both previously untreated and previously treated patients with metastatic Stage III or IV melanoma (Hodi et al., 2010; Robert et al., 2011). Increase in median survival was approximately 2 to 4 months, but >90% of patients eventually progressed. Ipilimumab (Yervoy®) is currently approved for metastatic or unresectable melanoma at a dose of 3 mg/ kg every 3 weeks.

2.5 PD-1 Checkpoint Inhibitors (Nivolumab and Pembrolizumab)

Two anti–programmed death 1 (PD-1) antibodies, nivolumab and pembrolizumab, were approved in 2014 by the Food and Drug Administration for the treatment of metastatic melanoma after progression during ipilimumab treatment and, in patients with BRAF-mutated melanoma, after progression during treatment with a BRAF inhibitor. These antibodies were associated with objective responses in 30 to 40% of patients. Two phase 3 trials have shown superior efficacy of nivolumab, as compared with chemotherapy, in previously untreated patients with wild-type BRAF tumors or in patients with either mutant or wild-type BRAF tumors after progression during ipilimumab therapy and, in patients with tumors positive for BRAF mutation, after progression during treatment with a BRAF inhibitor (Robert C, NEJM, 2015 and Weber JS, Lancet, 2015). Recently, pembrolizumab was associated with longer progression-free survival and overall survival and higher response rates than those associated with ipilimumab in a phase 3 trial involving patients with advanced melanoma (Robert C, NEJM, 2015).

In May 2015, results from the CheckMate 067 trial were presented. This study involving patients with previously untreated advanced melanoma, treatment with nivolumab alone or with the combination of nivolumab and ipilimumab resulted in significantly longer progression-free survival and higher objective response rates than did treatment with ipilimumab alone. The incidence of adverse events in this study was, in general, lowest in the nivolumab group and highest in the combination group.

Pembrolizumab was first evaluated in the large, phase 1 KEYNOTE-001 study (Robert C, Lancet, 2014). In a pooled analysis of 411 patients with advanced melanoma enrolled in KEYNOTE-001 and after a median follow-up duration of 18 months, the response rate was 34%, the response was maintained in 81% of those patients, and median overall survival was 25.9 months (Ribas A, 2014)

In KEYNOTE-006 PD-1 inhibition is compared with CTLA-4 blockade in a controlled, randomized trial involving patients with advanced melanoma. The estimated 6-month progression-free survival rates were 47.3% for patients receiving pembrolizumab every 2 weeks, 46.4% for those receiving pembrolizumab every 3 weeks, and 26.5% for those receiving ipilimumab. Median estimates of progression-free survival were 5.5 months (95% confidence interval [CI], 3.4 to 6.9), 4.1 months (95% CI, 2.9 to 6.9), and 2.8 months (95% CI, 2.8 to 2.9), respectively. One-year estimates of survival were 74.1% for patients receiving pembrolizumab every 2 weeks (hazard ratio for death as compared with the ipilimumab group, 0.63; 95% CI, 0.47 to 0.83; P<0.0005), 68.4% for those receiving pembrolizumab every 3 weeks (hazard ratio for death as compared with the ipilimumab group, 0.69; 95% CI, 0.52 to 0.90; P=0.0036), and 58.2% for those receiving ipilimumab (Roberts C, NEJM, 2015).

Based on these data, many clinician are changing practice patterns to use PD-1 inhibitors (nivolumab and pembrolizumab) as first line treatment in preference to ipilimumab.

2.6 Rationale for Combining Checkpoint Inhibitors with Dorgenmeltucel-L

Preclinical data have demonstrated synergy between vaccine approaches to cancer treatment and checkpoint inhibitors. In a murine model of melanoma, the combination of a whole cell vaccine and ipilimumab showed synergistic results (Holmgaard, NEJM, 2015). The goal of this study is to apply this approach to patients with metastatic melanoma, combining a HyperAcute immunotherapy whole cell vaccine with the immune checkpoints ipilimumab, nivolumab, or pembrolizumab.

3 PATIENT SELECTION

3.1 Eligibility criteria

Must be confirmed within 30 days prior to study enrollment/registration, except for β-HCG (confirm within 1 week) when appropriate. Subjects who are positive (+) for the BRAF mutation who have not received BRAF inhibitors yet, may be enrolled to this study based on the discretion of the treating physician and may receive BRAF inhibitors following this study.

Inclusion criteria**:**

- Histological/cytological diagnosis of melanoma.
- AJCC Stage IV (any T, any N, M1), metastatic, progressive, refractory, melanoma.
- Patients may have advanced unresectable Stage IV disease, resectable Stage IV disease, or recently resected Stage IV disease (<10 weeks prior) with no apparent disease (NAD)
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1 (see **Appendix B**).
- Serum albumin ≥3.0 gm/dL.
- Adequate organ function including:
  - Marrow: Hemoglobin ≥10.0 gm/dL, absolute granulocyte count (AGC) ≥1,000/mm^3, platelets ≥75,000/mm^3, absolute lymphocyte count ≥475/mm^3.
  - Hepatic: Serum total bilirubin ≤2.5 x upper limit of normal (ULN), ALT (SGPT) and AST (SGOT) ≤2.5 x ULN.
  - Renal: Serum creatinine (sCr) ≤ 1.5 x ULN.
- Prior therapy for melanoma that may include surgery, radiation therapy, immunotherapy including interleukins and interferon, and/or ≤2 different regiments of systemic chemotherapy, targeted therapy, or other experimental systemic therapies. Prior treatment with immune checkpoint inhibitors is not allowed (see Exclusion criteria).
- Patients must be ≥4 weeks since major surgery, radiotherapy, chemotherapy (6 weeks if they were treated with nitrosureas) or biotherapy/targeted therapies.
- Patients must have the ability to understand the study, its risks, side effects, potential benefits and be able to give written informed consent to participate. Patients may not be consented by a durable power of attorney (DPA).
- Male and female subjects of child producing potential must agree to use *contraception or avoidance of pregnancy measures* while enrolled on study and receiving the experimental drug, and for one month after the last immunization.

Exclusion criteria**:**

- Age <18-years-old.
- *Active* CNS metastases or carcinomatous meningitis. Patients with CNS lesions that have been treated and who have no evidence of progression in the brain on CT/MRI for ≥1 month are eligible.
- Pregnant or nursing women due to the unknown effects of immunization on the developing fetus or newborn infant.
- Other malignancy within five years, except that the following may be eligible:
  - patients curatively treated for localized squamous or basal cell carcinoma of the skin or for carcinoma *in situ* of the uterine cervix (CIN) or breast,
  - patients with a history of malignant tumor who have been disease free for at least five years and are not currently being treated.
- History of an allogeneic solid organ transplant or bone marrow transplant, or current active immunosuppressive therapy such as cyclosporine, tacrolimus, etc.
- Subjects taking systemic (parentally or orally) corticosteroid therapy for any reason, including replacement therapy for hypoadrenalism, are not eligible. Topical steroids are acceptable as are intranasal steroids.
- Active infection or antibiotics within 48 hours prior to study enrollment, including unexplained fever (temp > 38.1°C), if deemed clinically significant by the treating physician.
- Evidence of *active* autoimmune disease (e.g., systemic lupus erythematosis, rheumatoid arthritis, with the exception of vitiligo. Patients with a remote history of asthma or mild asthma are eligible.
- Other serious medical conditions that may be expected to limit life expectancy to less than 2 years (e.g., liver cirrhosis).
- Any condition, psychiatric or otherwise, that would preclude informed consent, consistent follow-up or compliance with any aspect of the study (e.g., untreated schizophrenia or other significant cognitive impairment, etc.).
- Patients having previously undergone splenectomy.
- Patients with known hepatitis or unstable liver disease, and/or positive serologies for Hepatitis B or C and HIV.
- Patients with sickle-cell anemia or thalassemia major.
- Subjects who received prior treatment with immune checkpoint inhibition consisting of ipilimumab, tremelimumab, nivolumab, pembrolizumab or other antibody to CTLA4 or PD-1.

*3.2 **Eligibility and On-Study Tests***

Baseline and on-study tests will include (see Section 8.0 Study Calendar):

- Baseline history and complete physical examination
- Serum chemistries including electrolytes, BUN, creatinine, calcium, glucose and albumin; liver function tests including total bilirubin, ALT (SGPT) AST (SGOT), LDH, and alkaline phosphatase; quantitative immunoglobulins (IgG, IgM, and IgE); CBC with platelets and differential.

- Thyroid stimulating hormone (TSH) and free T4.
- Pregnancy testing with serum β-HCG in women of child-bearing potential
- Blood (approximately 16 mL) for measurement of anti-αgal and anti-tumor antibodies to be drawn on Day 1 before treatment administration and as outlined in Section 8.
- For patients receiving the dorgenmeltucel-L immunotherapy, whole blood (approximately 10 mL) for replication competent retrovirus (RCR) testing on Day 1 prior to the first immunization and will be sent to NewLink Genetics.
- Contrast enhanced CT-scan of the chest and abdomen *or* whole body PET/CT fusion scan. CT-scan or MRI scan of the brain if known or suspected brain metastases. If indicated, CT scan of the neck, *or* ultrasound, PET-scan and/or radionucleide bone scan may also be obtained. PET scans and radionuclide bone scans may not be used for determination of response.
- Measurable disease or solid lesions, liver masses, lymph nodes and skin nodules will be measured and recorded pre-therapy using RECIST/irRC criteria.
- Whole blood (approximately 100 mL) in purple top tubes for PBLs for intracellular cytokines and ELISPOT to be drawn on Day 1 before treatment administration and as outlined in Section 8. These samples will be sent to NewLink Genetics for testing.

Baseline evaluations are to be conducted within 30 days prior to start of protocol therapy unless otherwise specified. In the event that the patient's condition has significantly deteriorated (e.g., significant increase in symptoms or worsening of ECOG PS), laboratory evaluations should be repeated within 5 days prior to initiation of therapy.

4 TREATMENT PLAN

4.1 ***Registration and Randomization***

All patients must be registered on study before beginning therapy. Treating physician must declare which immune checkpoint therapy will be used prior to enrolling a patient.

All subjects must have: (1) a signed Informed Consent Document and, (2) a completed Eligibility Checklist Form before registration on the study. To register a subject for this protocol, an authorized physician or their designee must FAX or EMAIL the subject information to the NewLink Genetics Registration Office or the site's designated CRA between the hours of 8:30 A.M. and 5:00 P.M. Central Standard Time, Monday through Friday. (FAX: [redacted] EMAIL: [redacted]). No evening, weekend or holiday registrations will be permitted. An online randomization process will be used to provide sites with treatment assignments for this study. A randomization plan will be provided to the sites detailing the process. Once eligibility and disease status stratum is confirmed by NewLink and the subject randomized, NewLink will FAX or EMAIL a confirmation of registration to the site. The treatment assignment will be provided to the site by EMAIL. The clinical site's storage facility/pharmacy will not release the immunotherapy until the day of the scheduled immunization.

A file of copies of all reports, laboratory studies and other pertinent information documenting the subject's eligibility for study will be maintained in the Clinical Research Office of NewLink Genetics Corporation.

4.2 Study Implementation

This study will be conducted in accordance with the procedures and polices established by CBER-FDA, Office of Biotechnology Assessment (OBA), the Institutional Biosafety Committee (IBC) and the IRB. The study and consent form will be discussed fully with each patient and informed written consent obtained.

Treatment must begin within 4-weeks of registration.

Study Agent Administration (see **Appendix C**)

The dorgenmeltucel-L immunotherapy cells will be injected intradermally (i.d.) using tuberculin or other small syringe with a #25-gauge needle. Injections will be administered as divided doses and administered on an alternating basis with each immunotherapy cycle given in the upper and/or lower extremities. Immunizations will be avoided within an extremity that has previously undergone a complete lymph node dissection.

Patients will be monitored before and after each injection by the nursing staff.

- Monitoring is to include: temperature (T), pulse (P), blood pressure (BP) and respiratory rate (R), measured within 30 minutes before administration of the immunotherapy, and then within 30 minutes after the immunization. In addition, patients will be monitored for signs of acute allergic reactions including local or disseminated skin rash and other adverse reactions.
- Should an adverse event occur after discharge, patients will be instructed to immediately contact the Principal Investigator, Associate Investigator or research nurse for further evaluation and/or treatment.
- Patients developing Grade 2 or greater acute adverse reactions will be monitored for an additional 1-2 hours or until the AE has resolved to less than Grade 2. Medically indicated treatment of the AE will be administered. If an acute AE of Grade 2 or greater persists for more than 4-hours despite observation and/or treatment, a decision on whether to continue observation, institute or modify treatment of the AE, or admit the patient to the inpatient unit for further observation and/or treatment will be made by the Principal Investigators or designees.

A detailed description of the immunotherapy, storage, handling and reconstitution for immunization may be found in Section 6.1.

4.3 Supportive Care

Patients are to be monitored during each immunization as described above in Section 4.2. Unexpected adverse events will be treated as medically indicated by the involved physicians. Complications of the patient's underlying melanoma or co-morbid medical conditions unrelated to the study treatment will be treated promptly by the study physicians with referral back to the patient's primary medical care provider as appropriate.

4.4 Duration of Therapy

Patients whose tumor progresses on therapy will be off-study. However, mild progression (≤25% increase in tumor size) at the beginning of the treatment is allowed, given the usual delayed response / pseudoprogression seen with immunotherapy (Wolchok et al., 2009).

Patients who experience a SAE which triggers stopping rules for immune checkpoint inhibitors ipilimumab, nivolumab, or pembrolizumab as described in their respective package inserts will be permanently discontinued from the immune checkpoint inhibitor. They can be continued on dorgenmeltucel-L (if in Arm 1) once recovered from immune checkpoint inhibitor toxicity.

Patients are also off study who:

- experience intercurrent illness that prevents further administration of treatment;
- decide to withdraw from the study;
- experience general or specific changes in the patient's condition that render them unacceptable for further treatment in the judgment of the investigator.

4.5 Off-Study Therapy Criteria

Patients will be removed from study therapy when any of the criteria listed in Section 4.4 applies. The reason for study removal and the date the patient was removed must be documented on the Case Report Form.

4.6 Post-Treatment Evaluation/Monitoring

For patients who receive the immunotherapy and complete or go off-treatment early, follow up visits will be made until 5 years or death whichever comes first.

Long-term Clinical Monitoring of Subjects Participating in this Gene Transfer Trial.
Subjects surviving for more than 2 years will be followed on a yearly basis for at least 13 additional years (15 years total) as recommended by the FDA Biologic Response Modifier's Advisory Committee (BRMAC) for late sequelae of gene transfer.

Information to be collected and made available to the FDA in the IND annual report and reports to other regulatory agencies as mandated will include:

- Clinical information on *de novo* cancers, neurological, autoimmune and hematological disorders.
- Unexpected medical problems, hospitalizations and medications.
- Expected or unexpected patient death and cause of death.

5 DOSING INFORMATION

The study is designed to evaluate the addition of dorgenmeltucel-L to standard of care checkpoint immunotherapy. The following information about ipilimumab, nivolumab, and pembrolizumab is provided as background and drawn from the package inserts of the respective immunotherapies. The information should not be considered complete nor comprehensive. The administration of

these agents (ipilimumab, nivolumab, and pembrolizumab) should be done at the direction of the treating physician according to the physician's usual standard of care practices.

5.1 Dorgenmeltucel-L Immunotherapy

Dorgenmeltucel-L immunotherapy consists of equal quantities of three cellular components. The cellular components (HAM-1, HAM-2, and HAM-3) of dorgenmeltucel-L immunotherapy have been derived from allogeneic melanoma cancer cell lines. HAM-1 is derived from the human melanoma cell line G361, HAM-2 is derived from the melanoma cell line SK-MEL28, and HAM-3 is derived from the human melanoma cell line COLO829. Master cell banks of these cellular components have been engineered to express the murine α(1,3)GT gene. During manufacturing the cells are amplified and harvested under sterile culture conditions then irradiated. The product is then stored in the vapor phase of liquid nitrogen until released for shipment. All production lots are subjected to testing to assure compliance with all product specifications before they are released for clinical use.

The immunotherapy cells (HAM-1, HAM-2, HAM-3) are supplied individually packaged in sterile 1.0 mL gasket-sealed cryovials. Each vial contains a cell suspension in a neutral saline solution with human albumin (USP) and glycerine (USP). After thawing, the content of the vials is a turbid yellow-white liquid. Injections must be administered within 30 minutes of thawing the immunotherapy.

For administration, each of the three immunotherapy cellular components is administered separately. Patients receive a total of six (6) injections per immunization procedure. The component specifications are listed in **Table 3** below.

Table 3. Immunotherapy Specifications

Dorgenmeltucel-L	Fill Volume	# Cells per Vial	Vial Size	Volume to be Injected	Volume per each Injection	Total Cells per Treatment	# of Injections
HAM1	0.65 mL	$6.5x10^7$	2 x 1.0 mL	1.0 mL	0.5 mL	100 M	2
HAM2	0.65 mL	$6.5x10^7$	2 x 1.0 mL	1.0 mL	0.5 mL	100 M	2
HAM3	0.65 mL	$6.5x10^7$	2 x 1.0 mL	1.0 mL	0.5 mL	100 M	2
TOTAL			**6 vials**	**3 mL**		**300 M**	**6**

The dose of dorgenmeltucel-L immunotherapy given in this study is 300 million HAM cells. When giving a dose of 300M HAM cells, the clinical site will give 6 injections (2 injections of 0.5 mL of HAM1 + 2 injections of 0.5 mL of HAM2 + 2 injections of 0.5 mL of HAM3).

The HAM immunotherapy cells are injected intradermally (i.d.) using a small (tuberculin) syringe with a #25-gauge needle. Injections are split between the forearms and thighs on a rotating basis at each immunization.

For preparation for injection see **Appendix C**.

Specific Risk/Adverse Events to HyperAcute immunotherapy

A number of patients receiving HyperAcute immunotherapy (for cancers of the lung, pancreas, and skin) experience skin reactions at the site of immunization. The types of inflammatory response observed varied among individuals. The following skin reactions have been observed:

A) Acute Reaction

In most cases, patients receiving HyperAcute immunotherapy experience a rapid inflammatory reaction at the site of injection. This reaction is characterized by swelling, erythema, heat in the area, mild discomfort and itching.

B) Delayed Type Hypersensitivity reactions

Some patients also experience a DTH-like reaction. In this case the inflammatory response takes two to three days to develop.

The following reactions have been observed during, immediately after an immunization, and/or 2-5 days later:

- Pain
- Erythema (Redness)
- Pruritus (Itching)
- Swelling
- Induration (Hardening)
- Irritation/Discomfort
- Warmness

To help alleviate any discomfort that the patient might experience, due to an adverse reaction at the injection site, the following treatment options are acceptable:

- First try ice or cold compresses to the area
- If itching/discomfort continues, diphenhydramine cream (or appropriate alternative anti-histamine cream) can be used
- If itching/discomfort is not alleviated with topical cream, oral diphenhydramine (or appropriate alternative anti-histamine) may be used
- Acetaminophen or ibuprofen can also be used for pain/discomfort

The most frequently reported HyperAcute-related adverse events (all grades) experienced in the Melanoma Clinical Trials 0104 and OCI-01 are injection site reactions, fatigue, and nausea.

For more details on adverse events observed, please see the Investigator's Brochure for dorgenmeltucel-L immunotherapy.

Procurement

The allogeneic dorgenmeltucel-L immunotherapy is prepared, vialed, supplied and shipped by NewLink Genetics Corporation. Dorgenmeltucel-L is shipped by air carrier to the clinical site on dry ice. Each shipment is accompanied by Clinical Investigational Material Shipment Receipt Form and a Certificate of Analysis for product safety testing. Upon receipt, at the clinical site, the product is unpacked by a designated person(s) and immediately transferred to the vapor phase of

a liquid nitrogen storage tank. The drug will be stored in the clinical site's Investigational Pharmacy or designated area in a monitored liquid nitrogen cryofreezer under strict QC conditions. The procedure for preparation is outlined in **Appendix C**.

Drug Accountability
FDA regulations require investigators to establish a record of the receipt, use, and disposition of all investigational agents. Investigators may delegate responsibility for drug ordering, storage, accountability and preparation to his/her designee. The investigator, or the responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received.

5.2 Ipilimumab (Yervoy®) – Information from package insert

Description
Ipilimumab (Yervoy) is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an igG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

Mechanism of Action
CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect, possibly through T-cell medicated anti-tumor immune responses.

Pharmacokinetics
The pharmacokinetics of ipilimumab was studied in 499 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg administered once every 3 weeks for four doses. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the curve (AUC) of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of YERVOY administered every 3 weeks, ipilimumab clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index of 1.5-fold or less. Ipilimumab steady-state concentration was reached by the third dose. The following mean (percent coefficient of variation) parameters were generated through population pharmacokinetic analysis: terminal half-life of 14.7 days (30.1%); systemic clearance (CL) of 15.3 mL/h (38.5%); and volume of distribution at steady-state (Vss) of 7.21 L (10.5%). The mean (±SD) ipilimumab C_{min} achieved at steady-state with the 3-mg/kg regimen was 21.8 mcg/mL (±11.2).

Specific Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 420 patients with melanoma who received single or multiple infusions of ipilimumab at doses of 0.3, 3, or 10 mg/kg. The effects of various covariates on ipilimumab pharmacokinetics were assessed in population pharmacokinetic analyses.

Ipilimumab CL increased with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a mg/kg basis. The following

factors had no clinically meaningful effect on the CL of ipilimumab: age (range 26 to 86 years), gender, concomitant use of budesonide, performance status, HLA-A2*0201 status, positive anti-ipilimumab antibody status, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined as there were insufficient numbers of patients in non-Caucasian ethnic groups.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater.

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels did not have a clinically important effect on ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment.

Pharmaceutical Data
Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab.

Supply
Ipilimumab is commercially available.

Specific Risk/Adverse Events with ipilimumab
Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediate reactions. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose. For specific details of toxicity management, the treating physician is instructed to refer to the package insert for ipilimumab and to follow the instructions and algorithms therein.

Specific attention to development of autoimmune events during periodic study visits can be evaluated by an optional checklist provided in **Appendix E**. This checklist in addition to the serologic tests obtained can be used by the study physicians to determine if further evaluation for autoimmune disease is warranted by an appropriate specialist in the organ system affected. This can be done to avoid misinterpretation of spurious autoimmune test results.

Trials using immunomodulatory agents such as ipilimumab CTLA-4 have shown a correlation between disease response and so called autoimmune breakthrough events (ABEs) like hypophysitis, colitis, autoimmune hepatitis, or dermatitis. It is for this reason that they are distinguished from other adverse events.

5.3 Nivolumab (Opdivo)

Description
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

Pharmacokinetics
The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Based on a population pharmacokinetic (PK) analysis using data from 909 patients, the geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Specific Populations: Based on a population PK analysis using data from 909 patients, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe impairment (TB greater than 3 times ULN and any AST).

Pharmaceutical Data
Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial. It is supplied in 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in single-use vials.

Supply
Nivolumab is commercially available.

Specific Risk/Adverse Events
Nivolumab can cause severe and fatal immune mediated adverse effects. Many organs systems can be involved. The most common severe adverse events include pneumonitis, colitis, hepatitis, nephritis, and thyroid disease (either hypothyroidism or hyperthyroidism). Additional immune mediated reactions observed include adrenal insufficiency, pancreatitis, neuropathies, hypophysitis, and Guillain-Barre syndrome.

Management of these conditions includes withholding of nivolumab, administration of high-dose corticosteroids, and if appropriate, initiation of hormone replacement therapy.

5.4 Pembrolizumab (Keytruda)

Description
Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Pharmacokinetics
The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18 to 94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m2;

n=210), moderate (eGFR 30 to 59 mL/min/1.73 m2; n=43), or severe (eGFR 15 to 29 mL/min/1.73 m2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment.

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

Supply
Pembrolizumab is commercially available.

Specific Risks / Adverse Events
Pembrolizumab can cause severe immune mediated adverse events and can involve multiple organ systems. Severe immune mediated adverse events include pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hypothyroidism and hyperthyroidism. Additional severe immune mediated adverse events can include dermatitis, uveitis, myositis, pancreatitis, and adrenal insufficiency.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids.

6 DOSING DELAYS/DOSE MODIFICATIONS

The dosing delay and modification information contained in this section concerning ipilimumab, nivolumab, and pembrolizumab is provided for background purposes. Dosing delays and / or modification of these agents should be performed consistent with standard of care practice by the treating physician within the guidelines provided in the respective package inserts.

6.1 Dosing Delays

A significant number of patients entered into clinical trials at the clinical sites live outside of the area including patients referred from across the United States. Due to potential scheduling or travel

difficulties, unrelated intercurrent illness, patient social or employment issues, weekends, government and other holidays, treatments may not be able to be administered on the planned protocol schedule. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts.

6.2 Dorgenmeltucel-L (HyperAcute-Melanoma) Dose Modifications

There is no provision made in this protocol for the reduction of the dose or other dosing modification of the immunotherapy treatment.

6.3 Ipilimumab Dose Modifications

The administration of ipilimumab under this protocol is to be within accordance with the package insert for ipilimumab. This includes toxicity management and dosing adjustments or discontinuation of ipilimumab. The following is intended to highlight aspects of management.

- Ipilimumab related toxicities must be resolved to baseline or ≤ Grade 1 prior to administering the next dose.
- No dose reductions for ipilimumab are allowed.
- Ipilimumab can be delayed if the reason for the delay is toxicity/AE and if resolved to Grade 1 or better can restart and continue every 3 weeks until all 4 planned doses are administered or 16 weeks from first dose, whichever occurs earlier.
- Please refer to the AE management algorithms provided by the package insert for ipilimumab on management of potentially ipilimumab-related adverse events (also in **Appendix D**).
- Liver function tests (AST, ALT total bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed within 3 days prior to dosing. Liver function test results must be reviewed by the principal investigator or designee prior to ipilimumab administration and meet dosing criteria specifications:
    - < 2.5 x ULN for AST and ALT and < 1.5 x ULN for total bilirubin
- If abnormal LFT values are detected, the subject must be managed using hepatotoxicity algorithm (see **Appendix D**).

Treatment may resume when the AE(s) resolve(s) to Grade 1 or baseline value.

During ipilimumab administration, ipilimumab must be permanently discontinued if the subject experiences any of the following toxicities. Events requiring permanent discontinuation are:

- Grade 3 or 4 motor or sensory neuropathy, regardless of causality
- Any AE which, in the judgment of the investigator, presents a substantial clinical risk to the subject with investigational drug dosing.
- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 or better severity with topical therapy or requires systemic treatment.
- Any other ≥ Grade 3 non-skin related AE with the exception of laboratory abnormalities and Grade 3 nausea and vomiting.
- Any Grade 4 laboratory abnormalities
- Persistent Grade 2 adverse reactions (that push ipilimumab administration beyond the

16 week window from first dose) or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.

- Severe of life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥ Grade 3)
  - AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous or hemorrhagic manifestations.
  - Severe motor or sensory neuropathy, Guillain-Barre syndrome, or myasthenia gravis.
  - Severe immune-mediated reactions involving any organ system (e.g. nephritis, pneumonitis, pancreatitis, myocarditis).
  - Severe infusion reaction (see Section 6.4)

6.4 Nivolumab Dosing Modifications

There are no recommended dose modifications for hypothyroidism or hyperthyroidism. Immune mediated adverse events should be treated with corticosteroids in accordance with the guidelines in the package insert.

Withhold nivolumab for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline
- Any other severe or Grade 3 treatment-related adverse reactions

Resume nivolumab in patients whose adverse reactions recover to Grade 0 to 1.

Permanently discontinue nivolumab for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 4 colitis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- Creatinine greater than 6 times ULN
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 1 or resolve within 12 weeks after last dose of nivolumab

6.5 Pembrolizumab Dosing Modifications

For immune mediated adverse reactions administer corticosteroids based on the severity of the reaction. See package insert for guidelines.

Withhold pembrolizumab for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Symptomatic hypophysitis
- Grade 2 nephritis
- Grade 3 hyperthyroidism
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume pembrolizumab in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue pembrolizumab for any of the following:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis
- Grade 3 or 4 nephritis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

6.6 Treatment of Checkpoint Inhibitor Related Infusion Reaction

Infusion reactions should be graded according to CTCAE version 4.03 Allergic reaction/ hypersensitivity criteria.

Severe infusion reaction requires permanent discontinuation for further treatment.

Appropriate medical therapy including fluids, epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions.

In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice.

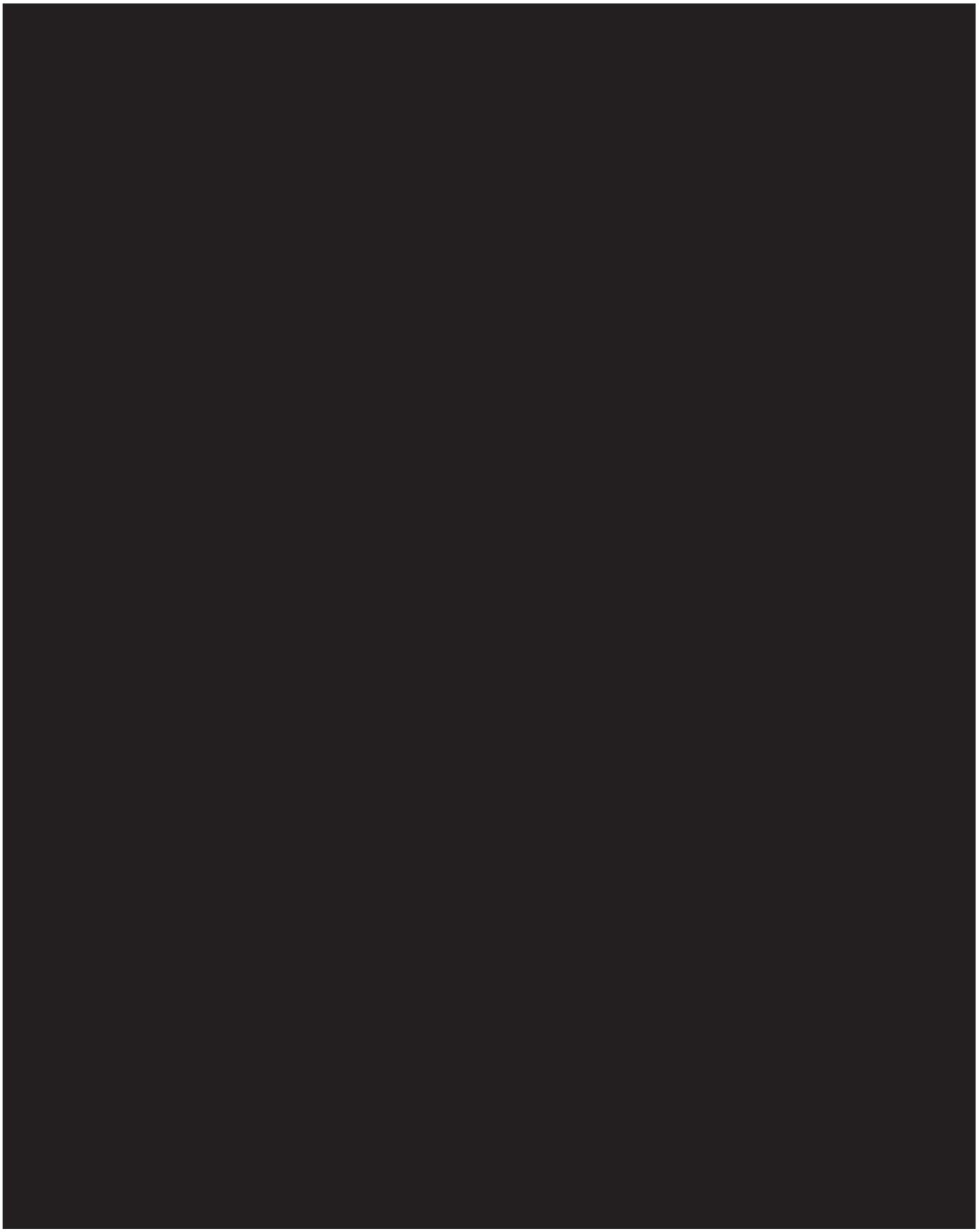
7 CORRELATIVE/SPECIAL STUDIES

7.1 *Parameters measured at baseline to evaluate subject's general immunological status*

[redacted]

7.2 Immunological monitoring during treatment and follow-up

[redacted]



8 STUDY CALENDARS

Study Calendar for Arm 1A (Ipilimumab plus Dorgenmeltucel-L Immunotherapy)
Ipilimumab 3 mg/kg IV given Q3 weeks x 4, dorgenmeltucel-L continues for up to 24 immunizations. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Mo 7	Mo 8	Mo 9	Mo 10	Mo 11	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	1ST FUV
	DAY	1	8	15	22	29	36	43	50	57	64	71	78	85	92	106	120	134	148	162	-	-	-	-	-	-	-	-	-	-	
HAM Injections		A	A	A	A		A		A		A		A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
Ipilimumab					X			X			X			X																	
Informed consent	X																													
Demographics	X																													
Medical history	X																													
Concurrent meds	X																													
Physical exam	X	X			X			X			X			X		X		X		----------Complete per SOC----------										X
Vital signs	X	X	X	X	X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																													
Weight	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X
Serum chemistry (with LDH)	B				B			B			B			B		B		B		B	B	B	B	B	B	B	B	B	B	B
b-HCG	C																														
TSH and Free T4	X				X			X			X			X																	
[redacted]		E												E						E						E				E	E
		F																													
		H						H						H					H				H			H		H		H	H
		I		I	I			I			I			I			I		I		I	I	I	I	I	I	I	I	I	I	I
		J						J			J																				
Radiologic Tumor (RECIST/iRRC) evaluation	X													X						X			X			X	X	X	X	X	X
AE/SAE Evaluation		----------Evaluate throughout Study and Follow Up Per Protocol----------																													

LEGEND FOR ALL STUDY CALENDARS:

A: Dorgenmeltucel-L (HyperAcute-Melanoma), 300 million HAM cells administered intradermally

B: Serum chemistries including BUN, creatinine, calcium, albumin, glucose, electrolytes, liver function tests including total bilirubin, ALT (SGPT) AST (SGOT), alkaline phosphatase and LDH. Should be drawn at the first follow-up visit and then as clinically indicated when subjects are in follow-up.

C: Serum or urine pregnancy test (Women of childbearing potential).

E: [redacted]

F: **For subjects receiving HAM immunotherapy:** Peripheral blood collection (10 mL purple top tube provided by NewLink Genetics) is to be sent same day, on room air, overnight express to NewLink Genetics for RCR testing for retrovirus. Draw prior to first immunization (Day 1) only.

H: [redacted]

I: [redacted]

J: [redacted]

1ST FUV: Please complete all procedures as outlined in the study calendars under 1st FUV.

Study Calendar for Arm 2A (Ipilimumab Alone)

Ipilimumab 3 mg/kg IV given Q3 weeks x 4, then evaluate disease. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	1ST FUV
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Ipilimumab		X			X			X			X				
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------X													
Physical exam	X	X			X			X			X				X
Vital signs	X	X			X			X			X			X	X
Height	X														
Weight	X	X			X			X			X				X
Performance status	X	X			X			X			X			X	X
CBC w/diff, plts	X	X			X			X			X			X	X
Serum chemistry (with LDH)	B	B			B			B			B			B	B
B-HCG	C														
TSH and Free T4	X	X			X			X			X			X	
[redacted]		E												E	E
		H						H							H
		I			I			I			I			I	I
		J						J			J				
Radiologic Tumor (RECIST/iRRC) evaluation	X													X	X
Adverse event evaluation		X----------X													X

Study Calendar for Arm 1B (Nivolumab plus Dorgenmeltucel-L)

Nivolumab 240 mg Q2 weeks until disease progression or significant toxicity, dorgenmeltucel-L continues for up to 24 immunizations. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Mo 7	Mo 8	Mo 9	Mo 10	Mo 11	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	1ST FUV
	DAY	1	8	15	22	29	36	43	50	57	64	71	78	85	92	106	120	134	148	162	-	-	-	-	-	-	-	-	-	-	
HAM Injections		A	A	A	A		A		A		A		A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
Nivolumab					X		X		X		X		X		X	X	X	X	X	X	---Continue every 2 weeks with Nivolumab---										
Informed consent	X																														
Demographics	X																														
Medical history	X																														
Concurrent meds	X	X----------X																													
Physical exam	X	X			X				X				X			X		X			----------Complete per SOC----------										X
Vital signs	X	X	X	X	X		X		X		X		X		X	X	X	X	X	X	---Continue every 2 weeks with Nivolumab---										X
Height	X																														
Weight	X	X			X				X				X			X		X		X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X			X		X		X		X		X		X	X	X	X	X	X	---Continue every 2 weeks with Nivolumab---										X
CBC w/diff, plts	X	X			X		X		X		X		X		X	X	X	X	X	X	---Continue every 2 weeks with Nivolumab---										X
Serum chemistry (with LDH)	B				B		B		B		B		B		B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B
b-HCG	C																														
TSH and Free T4	X				X				X				X			X		X		X	---Obtain at least monthly with Nivolumab---										
[redacted]		E													E					E						E				E	E
		F																													
		H							H						H				H				H			H		H		H	H
		I		I	I				I		I				I		I		I		I	I	I	I	I	I	I	I	I	I	I
		J					J				J																				
Radiologic Tumor (RECIST/iRRC) evaluation	X														X					X			X			X	X	X	X	X	X
AE/SAE Evaluation		----------Evaluate throughout Study and Follow Up Per Protocol----------																													

Each Subsequent Cycle:

Days 1 and 15 – Nivolumab 240 mg given IV; Obtain VS, PS, CBC, Chemistries

Day 1 – TSH and Free T4, Weight

Study Calendar for Arm 2B (Nivolumab Alone)

Nivolumab 240 mg Q2 weeks until disease progression or significant toxicity Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	1ST FUV
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Nivolumab		X		X		X		X		X		X		X	
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------X													
Physical exam	X	X													X
Vital signs	X	X		X		X		X		X		X		X	X
Height	X														
Weight	X	X				X				X				X	X
Performance status	X	X		X		X		X		X		X		X	X
CBC w/diff, plts	X	X		X		X		X		X		X		X	X
Serum chemistry (with LDH)	B	B		B		B		B		B		B		B	C
B-HCG	C														
TSH and Free T4	X	X				X				X				X	
[redacted]		E												E	E
		H						H							H
		I		I		I				I				I	I
		J						J				J			
Tumor measurements	X													X	X
Radiologic (RECIST/iRRc) evaluation	X													X	X
Adverse event evaluation		X----------X													X

Each Subsequent Cycle:

Days 1 and 15 – Nivolumab 240 mg given IV; Obtain VS, PS, CBC, Chemistries

Day 1 – TSH and Free T4, [redacted] (monthly x 8, every 3 months x 4), Weight

Study Calendar for Arm 1C (Pembrolizumab plus Dorgenmeltucel-L)

Pembrolizumab 2 mg/kg given Q3 weeks until disease progression or significant toxicity, dorgenmeltucel-L continues for up to 24 immunizations. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Mo 7	Mo 8	Mo 9	Mo 10	Mo 11	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	1ST FUV
	DAY	1	8	15	22	29	36	43	50	57	64	71	78	85	92	106	120	134	148	162	-	-	-	-	-	-	-	-	-	-	
HAM Injections		A	A	A	A		A		A		A		A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
Pembrolizamub					X			X			X			X	----------Continue Pembrolizamub every 3 weeks----------															
Informed consent	X																														
Demographics	X																														
Medical history	X																														
Concurrent meds	X	X----------X																													
Physical exam	X	X			X			X			X			X		X		X		----------Complete per SOC----------										X	X
Vital signs	X	X	X	X	X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																														
Weight	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X			X			X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry (with LDH)	B				B			B			B			B		B		B		B	B	B	B	B	B	B	B	B	B	B	B
b-HCG	C																														
TSH and Free T4	X				X			X			X			X		X		X		----Obtain at least monthly during Pembrolizamub										
[redacted]		E																		E						E				E	E
		F																													
		H						H						H					H				H			H		H		H	H
		I		I	I			I			I			I			I		I		I	I	I	I	I	I	I	I	I	I	I
		J						J			J																				
Radiologic Tumor (RECIST/iRRC) evaluation	X													X						X			X			X	X	X	X	X	X
AE/SAE Evaluation		----------Evaluate throughout Study and Follow Up Per Protocol----------																													

Each Subsequent Cycle:

- Pembrolizumab 2 mg/kg IV given every 3 weeks
- VS, PS, CBC, Chemistries completed every 3 weeks while receiving Pembrolizumab
- TSH and Free T4 completed at least monthly while receiving Pembrolizumab
- [redacted]
- Imaging for disease evaluation completed every 3 months

Study Calendar for Arm 2C (Pembrolizumab Alone)

Pembrolizumab 2 mg/kg given Q3 weeks until disease progression or significant toxicity. Study visits may be performed +/- 3 days from the targeted study visit date to allow for holidays and other scheduling conflicts. Follow-up visits may be performed +/- 2 weeks from the targeted study visit date.

EVALUATIONS	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	1ST FUV
		D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85	
Pembrolizumab		X			X			X			X			X	
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------X													
Physical exam	X	X			X			X			X			X	X
Vital signs	X	X			X			X			X			X	X
Height	X														
Weight	X	X			X			X			X			X	X
Performance status	X	X			X			X			X			X	X
CBC w/diff, plts	X	X			X			X			X			X	X
Serum chemistry (with LDH)	B	B			B			B			B			B	B
B-HCG	C														
TSH and Free T4	X	X			X			X			X			X	
[redacted]		E												E	E
		H						H							H
		I			I			I			I			I	I
		J						J			J				
Tumor measurements	X													X	X
Radiologic (RECIST/iRRc) evaluation	X													X	X
Adverse event evaluation		X----------X													X

Each Subsequent Cycle:

- Pembrolizumab 2 mg/kg IV given every 3 weeks
- VS, PS, CBC, Chemistries, TSH and Free T4, [redacted] (monthly x 8, every 3 months x 4)
- Imaging for disease evaluation completed every 3 months

Follow Up Visits for ALL Subjects (after 1st FUV):

- Imaging to be completed every 3 months until disease progression, after disease progression imaging is completed per standard of care
- Survival status checks to be completed at least every 3 months until death or lost to follow up
- All other assessments should be completed per standard of care practices.

9 MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

Each time a tumor assessment occurs, response and progression will be evaluated in this study using both the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] as well as immune-related response criteria (irRC). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Criteria for immune-related response criteria are described later in this section.

Tumor assessments will be performed approximately every 3 months in all treatment arms.

Definitions
Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with ipilimumab or dorgenmeltucel-L.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters
Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray or as $\geq$10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI varies globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is

mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Any responses must be confirmed by repeat tumor assessment at least 4 weeks after initial documentation. Any suspected progression with < 25% increase in tumor size or the appearance of new lesions will not immediately count as progression but will be evaluated according to irRC (see below).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Immune-related Endpoints

The irRC incorporates several elements reflecting the complex tumor dynamics of ipilimumab treatment. Under these criteria, a measure of tumor volume is used that incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear. New lesions alone do not qualify as irPD.

In this study, irRC will be used to assess subject response to study treatment per investigator assessment. The endpoint irPFS will be determined based on investigator assessment. In order to adequately address this objective, investigators will obtain confirmatory scans beyond RECIST PD and follow the instructions in this section for the determination of immune-related response.

New Lesion Measurement

The irRC are tumor assessment criteria that have been developed to better capture the activity of immunotherapeutic agents.[23] These criteria have been used with success in clinical studies that were performed with ipilimumab in advanced metastatic melanoma and in lung cancer.

Additional tumor response data will be collected, beyond what is required to apply the RECIST criteria. More specifically, the investigator will have to record in the CRF the bi-dimensional measurements for each new lesion which has become measurable in each tumor assessment.

To support evaluation of progression-free survival based on irRC criteria (irPFS) in this indication, investigators must perform tumor assessments (including new lesion measurements) during the Toxicity/Progression Follow-up Phase in subjects who have experienced RECIST progression until the total sum of product diameters (SPD including new lesions) has increased 25% or more from the nadir or until subjects discontinue study therapy regardless of whether the subject is initiating subsequent therapy. All available post RECIST progression tumor imaging- based assessments during this phase in the study must be entered into the CRF, including any standard of care assessments and any assessments performed while under non-study subsequent cancer therapy.

Any subject who develops an objective tumor response (CR or PR) or progression (PD) is required to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding. Sites are encouraged to collect additional CT scans after RECIST PD has been confirmed, as long as a subsequent line of therapy has not been initiated.

Definition of Tumor Response Using irRC
Calculation of Immune-related Sum of Products of Diameters (irSPD)

The irSPD incorporates measurable new lesions that may have developed on-study, providing an assessment that includes both index and new lesions. The tumor assessment performed during Screening will serve as the baseline for determination of tumor response using irRC.

irSPD at Baseline: The sum of the product of the diameters for all index lesions identified prior to randomization. At baseline, irSPD and SPD are the same.

irSPD at TA: For every post-randomization TA collected, per protocol Section 5.1 or as clinically indicated including post mWHO PD TA, the irSPD at TA will be calculated using tumor imaging scans. Both index lesions and any measurable new lesions that have developed on study will be included.

irSPD Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the irSPD (irSPD Baseline or irSPD at TA) is used to classify subsequent TAs for each subject. Because ipilimumab treatment may result in complex tumor dynamics in which index lesions may shrink while new lesions appear, the irSPD nadir may be different from the SPD nadir, and may occur either before or after the SPD nadir.

At baseline, the irSPD is measured and recorded.

At each subsequent assessment timepoint, a separate assessment of timepoint overall response will be obtained for that timepoint. The sum of products of perpendicular diameters calculated and recorded at each post-baseline timepoint for immune-related response purposes (irSPD) include measurements of index lesions and also include measurable new lesions which are not too small to measure at this timepoint. A value of 25 mm2 (5 mm x 5 mm) is imputed for each index and previously measurable new lesion which is present but too small to measure.

Timepoint Overall Response Using irRC

- The overall assessment of immune-related response reported at each timepoint will be based on the following criteria:
- Immune-related CR (irCR): Complete disappearance of all tumor lesions (index and non-index together with no new measurable/unmeasurable lesions).
- Immune-related PR (irPR): A decrease, relative to baseline of the irSPD (as defined above) of 50% or greater is considered an irPR.
- Immune-related SD (irSD): irSD is defined as an evaluable response that fails to meet criteria for immune-related CR or immune-related PR, in the absence of irPD.
- Immune-related Progressive Disease (irPD): At least a 25% increase in the irSPD (based on irSPD of all index lesions and any measurable new lesions, as defined above) over the nadir irSPD, or the occurrence of any new measurable lesions if the SPD nadir is "0" (including when no measurable lesions are present at baseline.
- Immune-related Unknown Response (irUN): Tumor assessments which cannot be evaluated (e.g., due to image quality, inability to assess all relevant lesions, etc.) will be reported as irUN.

10 REGULATORY AND REPORTING REQUIREMENTS

10.1 ***Subject Data***

Subject data accrued on this study will be reported in accordance with 21CFR 312.32.

10.2 ***CTCAE***

This study will utilize the CTCAE Version 4.03 for Adverse Event (AE) Reporting. The CTCAE v4.03 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

10.3 ***Notifications***

The P.I. will notify the IRB, OBA, and NewLink Genetics (Study Sponsor) who in turn will notify the FDA and other regulatory agencies of all serious adverse events as required by law or regulation. All participating investigators will be notified of IND Safety Reports by *Investigator Alerts* sent through email.

10.4 ***Definitions for Reporting Purposes***

In this protocol the study drug dorgenmeltucel-L is being combined with one of three different immune checkpoint immunotherapies, drugs with an established safety profile. Adverse events and serious adverse events observed during the course of this trial and previously reported as related to ipilimumab, nivolumab, or pembrolizumab will be attributed to such. Adverse events previously seen with dorgenmeltucel-L or other HyperAcute therapies will be attributed to dorgenmeltucel-L. Novel serious adverse events not previously seen with any study agent will initially be considered regimen associated and will require an evaluation by the PI and the sponsor

to determine attribution. This will be done via teleconference within three business days of the report.

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Related to the use of the drug: There is a reasonable possibility (more likely than not) that the experience may have been caused by the investigational drug.

A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

10.5 ***Reporting Form and Content***

For those events that meet the criteria in Section 10.6 below, please complete the **Serious Adverse Event Reporting Form.** This form will be provided by NewLink Genetics. Please send to NewLink Genetics within the time frames listed below. Please FAX to [redacted] to [redacted] Please call [redacted] with any reporting questions. You may also contact and send this form to the CRA designated for your site.

10.6 ***Reporting Requirements for Serious Adverse Events (21 CFR Part 312)***

Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events within 24 hours of learning of the SAE, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered SERIOUS if it results in ANY of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.

6. Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

SAE reporting timelines are defined as:

- "24 Hour; 5 Calendar Days" – The SAE must initially be reported within 24 hours of learning of the SAE, followed by a complete SAE report within 5 calendar days of the initial 24 hour report.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite to dorgenmeltucel-L require reporting on the same timelines as noted above.

Deaths clearly due to progressive disease should **NOT** be reported expeditiously but rather should be reported via routine reporting

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported through expedited SAE reports must also be reported in routine study data submissions (CRFs).

Adverse Event Case Report Form

All adverse events (regardless of grade and attribution) observed while on study and for 30 days after last dose of treatment, must be recorded on the adverse event case report form. After 30 days from last dose of treatment, only adverse events that are related to the study drug/combination are required to be recorded on the adverse event forms.

Reporting Requirements for Baseline Adverse Events:

A pertinent positive finding identified on baseline assessment is to be documented as a Baseline Adverse Event using CTCAE terminology and grade on the provided Baseline CRF. An expedited

AE report is not required if a patient is entered on to the study with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the trial and reported if it fulfills expedited AE reporting guidelines.

1) If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
2) If the AE resolved and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
3) No modification in grading is to be made to account for abnormalities existing at baseline.

Other Reporting Requirements:
In addition to the clinical monitoring as outlined in the Study Calendars, monitoring for long-term or delayed adverse events related to gene transfer (required at least yearly for 15 years by the FDA-BRMAC) will be the responsibility of the Principal Investigator at each site. Each PI will be responsible for the recording and reporting of this information to the sponsor. Investigators must report the emergence of new clinical conditions, specifically:

1) New malignancy(ies);
2) New incidence or exacerbation of a pre-existing neurologic disorder;
3) New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder;
4) New incidence of a hematologic disorder;
5) Unexpected illness and hospitalizations;
6) Expected or unexpected death and cause of death.

For the first 5 years, we recommend that Principal Investigators schedule a visit with each study subject to record new findings including history, physical examination, or laboratory testing at least once a year, even if the subject is off study. For the subsequent 10 years, we recommend that Investigators contact subjects by telephone or written questionnaire at least once a year to gather new information.

11 Human Subjects Protections

11.1 *Rationale for Subject Selection*

Melanoma is a common cancer that affects both genders and all racial/ethnic groups. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. We will make an attempt at enrolling representative proportions of women and minorities on this study. However, darker skin pigmentation is a significant protective factor for the development of melanoma. The incidence of melanoma in Blacks is more than 30-fold lower than Caucasians. This would necessarily mean that African-Americans and other ethnic groups with darker skin pigmentation will be under represented in patients eligible for this study.

To date, there is no information that suggests differences in immunization or disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this phase 2 study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. In this small phase 2 trial it is unlikely that significant differences in outcome would be detected that correlate with gender or racial/ethnic identity. If differences in

outcome that correlate to gender or to racial/ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

11.2 ***Participation of Children***

The occurrence of melanoma in individuals less than 18 years of age is rare and usually associated with congenital dysplastic nevus syndromes. Minors below the age of 18 will not be eligible for this protocol because of the limited information available on the effects and toxicity of anti-tumor vaccines in children, in particular the extremely limited information concerning allogeneic expression of α(1,3)GT in adults, and the complete lack of safety information on these reagents in children.

11.3 ***Evaluation of Benefits and Risks***

The benefits of this immunization approach are theoretical and it is hoped that the induction of an acute rejection response to the α(1,3)galactosylated residues on the allogenic melanoma cancer cells used to immunize the patient will lead to cross-recognition of weak native tumor antigens on the patient's melanoma cells that may be shared with the genetically engineered immunotherapy cells. By generating an antibody and cellular immune response against the patient's tumor, it is hoped that the patient may benefit by a tumor response.

Given the safety demonstrated with transfer of murine retroviral vector producer cells in several studies that naturally express the α(1,3)GT enzyme and have 1,3-α-galactosylated residues, and the poor prognosis of this patient population, it is believed that the possible benefits from tumor response and improved survival probability far outweigh the risk to the patient. The information obtained in this study may be extremely valuable in the treatment of melanoma and other malignancies in the future. The patients to be entered in this protocol have refractory or recurrent melanoma and limited life expectancies. The chance of this experimental treatment to provide clinical benefit is unknown. All possible benefits and known risks will be carefully explained to all patients and an Informed Consent Document will be signed by the patient prior to entrance into the protocol.

There are no anticipated serious adverse side effects to the immunization technique employed in this study. Theoretical risks may include the induction of unanticipated autoimmune disease and/or liver, kidney, lung, heart and CNS damage and/or coagulopathy and bleeding as a result of excessive activation of the complement (C') system. Expected risks and discomforts to the patients are minimal and will be those of needle sticks and phlebotomy. An acceptable adverse event profile was developed in the Phase I part of the trial. Patients will be observed for one hour after each immunization for allergic/hypersensitivity reactions. Patients will be treated as deemed medically appropriate for any immediate or delayed adverse event related to the immunization.

Five similar instances involved the development of an aggressive T-cell acute lymphocytic leukemia (T-ALL) that contain a vector proviral insertion at a chromosomal translocation breakpoint in three children that underwent *ex vivo* transduction of CD34+ hematopoeitic stem cells with a Moloney-based retroviral vector in a clinical trial for the treatment of X-SCID. While most children who participated in this clinical trial appear to have been cured of their disease (18 out of 20), five children developed the leukemia approximately 2 to 5 years after their gene

therapy treatment. Extensive testing was done to determine the cause of the leukemia, and it was found that the virus used to deliver the X-SCID gene disrupted a normal gene in the bone marrow cells that then lead to the development of leukemia. One of these children has since died of their leukemia, and the long-term prognosis of the other children is unknown at this time.

These AE's are not believed to be relevant to the present trial. This trial involves neither the use of adenoviruses, the direct administration of live retrovirus, or live transduced cells to the patient. The *ex vivo* allogeneic immunotherapy cells transduced by our vector are nonviable after being irradiated.

11.4 ***Consent Processes and Documents***

All patients will be thoroughly screened prior to admission onto this study. During this time, the patient, along with family members, will be presented with a detailed description of the protocol treatment. The specific requirements, objectives, risks and benefits will be reviewed with the patient. The Informed Consent document will be given to the patient and they are asked to review it and ask questions prior to agreeing to participate in this protocol. The patient will be reassured that participation on this trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences. The Principal Investigator or their designee is responsible for completing the consent process and a copy of the completed Consent Document is offered to the patient.

11.5 ***Recruitment Strategy***

Patients, their physicians or family members may contact the Principal Investigator or a designated associate investigator responsible for this protocol. Given the large number of patients with melanoma and the limited therapy available for advanced disease, we believe recruitment for this trial will be rapid. An IRB approved informational mailing announcing the availability of this study will be sent to the clinical oncology community. The study will be registered with the clinicaltrials.gov website database.

11.6 ***Patient Confidentiality***

Strict patient confidentiality is standard policy at the participating clinical sites. Standard practices will be strictly followed and adhered to.

12 STATISTICAL CONSIDERATIONS

12.1 ***Sample Size***

This study was originally designed to compare the response rates between the combined dorgenmeltucel-L plus immune checkpoint therapy arm to the immune checkpoint therapy arm alone. During this study, enrollment will include a total of 100 evaluable patients across 2 treatment arms (50:50).

Assuming a disease control rate of 22% (Wolchok *et al.*) in the immune checkpoint monotherapy arm and a combined arm response rate of 42%, a total of 100 patients (1:1 ratio) will be required to assess superiority of response rate with 80% power and two-sided alpha of 0.20.

As the primary endpoint has been changed from overall response rate to PFS, 50 patients per treatment arm (100 patients total) will provide 70% power to detect a hazard ratio of 0.6895 and 80% power to detect a hazard ratio of 0.6435, assuming the immune checkpoint monotherapy control arm has a median time to disease progression of 3 months and a two-sided type I error rate of 0.20. A total of 96 events are required for analysis.

12.2 Blinding and Randomization

This is an open-label, randomized study. Patients will be randomized to receive immune checkpoint therapy plus dorgenmeltucel-L or immune checkpoint therapy alone in a 1:1 ratio. Patients enrolled in this and later protocol amendments will be stratified by treatment choice and disease status and categorized as follows:

1) Patients with unresectable advanced disease
2) Patients with resectable advanced disease who receive the immunotherapy in advance of resection
3) Patients with resected isolated advanced disease who are treated in a no apparent disease (NAD) state

With sufficient sample size enrolled per disease status category, the randomization process is designed to provide balance between the two treatment arms within each of the disease status categories. The number of patients in each stratum will not be restricted.

Patients enrolled in Protocol Version 1 were not stratified; however the disease status criteria of these patients will be collected to properly account for the randomization strata in the statistical analysis. Further details regarding the randomization procedure are available in the Randomization Plan.

12.3 Statistical Methodology

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the numbers and percentages of patients within each category (with a category for missing data) of the parameter will be presented. Percentages will be based on non-missing data. For continuous variables, the number of subjects, mean, median, standard deviation (StdDev), minimum, and maximum values will be presented. Time-to-event data will be summarized using 25th, 50th (median), and 75th percentiles with associated 2-sided 80% confidence intervals, as well as percentage of censored observations. Quartiles and confidence intervals will be estimated using product-limit (Kaplan-Meier) methodology.

Populations to be Analyzed

The primary population for efficacy will be the full analysis set (FAS), defined as all randomized subjects. In the FAS patients will be analyzed in the treatment group to which they were assigned.

The primary population for safety analyses will be the safety analysis set, defined as all randomized subjects who receive at least one administration of study treatment (dorgenmeltucel-L or immune checkpoint therapy).

Demographic and Baseline Characteristics

Demographic and baseline disease characteristic data summarization will be performed in order to descriptively assess the comparability of dose groups. Data to be tabulated will include sex, age, and race, as well as disease-specific information.

Efficacy Analyses

The primary efficacy endpoint is PFS, where disease progression is defined according to RECIST v1.1. Progression free survival will be summarized using the Kaplan-Meier method of estimation, including the 25^{th}, 50^{th}, and 75^{th} percentiles of time to progression with 95% confidence intervals. Kaplan-Meier plots will be produced by disease status strata to examine the difference in response rates between treatment groups. A stratified log rank test will be applied to test for treatment effect on PFS.

Overall response rate is defined as subjects with a best overall response of at least stable disease. Subjects' best overall response, as determined by the investigator from RECIST, will be summarized by presenting the numbers and percentages of subjects in each response category. The overall response rate will be summarized similarly. Ninety-five percent confidence intervals (CIs) will be constructed for the overall response rate.

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) according to RECIST v1.1 until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Duration of overall response will be analyzed in a similar manner to PFS.

Duration of stable disease is measured from the start of the treatment until the criteria for progression are met according to RECIST v1.1, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. Duration of stable disease will be analyzed in a similar manner to PFS.

Overall survival is defined as the time to death or last contact and will be summarized in a similar manner to PFS.

As additional secondary endpoints, analysis of PFS, overall response rate, duration of overall response, and duration of stable disease will be repeated using the irRC criteria to identify disease response.

Longitudinal immunological measurements will be analyzed using linear mixed model regression analysis to examine the changes in immunological measurements over time as well as to understand differences between treatment groups in immunological responses over time. An interaction term between disease status category and treatment group will be tested to determine if there is a differential association between strata.

Multiplicity Issues
No adjustments for multiple comparisons are required for the primary efficacy analysis, since a single primary outcome variable has been specified. No formal hypothesis testing will be applied to the secondary efficacy endpoints.

Missing Data
In general, there will be no substitutions made to accommodate missing data points. All data recorded on the case report form will be included in data listings that will accompany the clinical study report. For analysis of time to event endpoints, subjects who have no efficacy evaluations will be considered censored at time 0. Imputation rules for specific efficacy endpoints will be detailed in the statistical analysis plan.

Safety Analyses
Adverse events will be summarized by MedDRA system organ class and preferred term. Separate tabulations will be produced for all treatment-emergent adverse events, treatment-related adverse events (those considered by the Investigator as at least possibly drug related), serious adverse events, discontinuations due to adverse events, and adverse events of at least Grade 3 severity. By-patient listings will be provided for deaths, serious adverse events, and events leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory data and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study.

In addition, shift tables of laboratory data from baseline to worst value on treatment will be presented based on CTCAE v 4.03 grading.

13 Administrative and Regulatory Considerations

13.1 Regulatory Compliance/Good Clinical Practices

This study will be conducted in accordance with the following regulations and guidelines, to include but not limited to:

- Declaration of Helsinki (October 2000)
- Current ICH Guideline for Good Clinical Practice
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application
- Dear Gene Therapy IND or Master File Sponsor Letter-3/6/2000
- Dear Gene Therapy IND Sponsor/Principal Investigator Letter 11/5/1999
- Letter to Sponsors/Researchers-Human Cells Used in Therapy Involving the Transfer of Genetic Material by Means Other Than the Union if Gamete Nuclei-7/6/2001
- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy-3/30/1998

13.2 Regulatory Documentation

Prior to study start-up, investigators will collect the following documents, as outlined in the Essential Documents Section 8.0 of the ICH Guidelines for Good Clinical Practice:

- Signed Confidentiality Agreement
- Signed Clinical Trial Agreement, if applicable
- Up-to-date signed and dated Curriculum Vitae and copies of medical licenses for all investigators to be submitted promptly
- Financial Disclosure form for Principal and one sub/co-investigator with financial disclosure forms for all investigators to be submitted promptly
- FDA Form 1572
- IRB approval to conduct the study: IRB-approved Informed Consent Form
- Name and address of the IRB with the statement that it is organized and operates according to GCP and the applicable laws and regulations
- IRB membership roster
- Local laboratory certifications, its name and address
- Local laboratory normal ranges (a dated copy for tests to be performed during the study)
- Financial agreement, if applicable
- Signed and dated Investigator Agreement page of the final protocol and amendments, where applicable

13.3 Institutional Review Board (IRB)

This trial will be undertaken only after full approval of the protocol and addenda has been obtained from a local IRB and a copy of this approval has been received by the sponsor. The IRB must be informed of all subsequent protocol amendments issued by the sponsor. Reports on and reviews of, the trial and its progress will be submitted to the IRB by the investigator at intervals set force in its guidelines.

13.4 Informed Consent

Each patient must give written consent and sign other locally required documents after the nature of the study has been fully explained. The informed consent form must be signed prior to performance of any study-related activity. The informed consent form that is used must be approved both by the sponsor and by the reviewing IRB. The Informed Consent should be in accordance with the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practices (GCP) guidelines.

13.5 Administrative Requirements

Protocol modifications
The investigator will not modify this protocol without obtaining permission from the sponsor. All protocol amendments must be issued by the sponsor, signed and dated by the investigator, and should not be implemented without prior IRB approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative

aspects of the trial (e.g., change in monitor(s), change of telephone number(s). In situations requiring a modification, the investigator or other physician in attendance will contact the medical monitor by fax or telephone (see Contact Information page). This contact must be made prior to implementing any departure from protocol. Contact with the sponsor must be made as soon as possible in order to outline an appropriate course of action.

Record Retention

In compliance with the ICH/GCP guidelines the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements.

Case Report Form (CRF) Completion

CRFs are provided for each patient. Data must be entered onto CRFs in English. All forms must be filled out in black ball-point pen. CRFs must be signed by the investigator where indicated.

All CRF corrections are to be made by the investigator or other authorized study center personnel as instructed on the CRF title page. The investigator must authorize changes to the recorded safety and efficacy data.

Monitoring

NewLink Genetics (sponsor) will perform on-site monitoring visits as outlined in the Monitoring Plan for this clinical trial. The dates of the visits will be recorded by the monitor in a trial center, with the monitor visitor's log to be kept at the site. The first routine monitoring visit will usually be made within 4 weeks after enrollment has begun at that site. At these visits the monitor will verify the data entered onto the CRFs with the hospital or clinic records (source documents) and follow the procedures as outlined in NewLink Genetics SOPs. At a minimum, source documentation must be available to substantiate patient eligibility and participation, proper informed consent procedures, adherence to protocol procedures, record of safety and efficacy parameters, adequate reporting and follow-up of adverse events, administration of concomitant medication, drug receipt/dispensing/return records, study medication administration information, and date of completion and reason. Specific items required as source documents will be reviewed with the investigator prior to the study. Findings from this review of CRFs and source documents will be outlined in a Site Visit Report and discussed with the investigator. The sponsor expects that, during monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documents will be available, and a suitable environment will be provided for review of study-related documents.

Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators, review of protocol procedures with the investigator and associated personnel prior to the study, and periodic monitoring visits by the sponsor. CRFs will be reviewed for accuracy and completeness by the sponsor during on-site monitoring visits and after return of CRFs to the

sponsor any discrepancies will be resolved with the investigator or designees per NewLink Genetics SOPs.

On-Site Audits

Representatives of the sponsor's Clinical Quality Assurance department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. All efforts will be made to preserve patient privacy. Sufficient prior notice will be provided to allow the investigator proper preparation for the audit. Auditing procedures may also be conducted by any regulatory body. The investigator should immediately notify the sponsor about any audit.

Use of Information and Publication

All information on HyperAcute cancer immunotherapy, NewLink operations, patent application, manufacturing process, basic scientific data supplied by the sponsor to the investigator and not previously published is considered confidential and remains the sole property of NewLink Genetics. The investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The investigator understands that the information developed in the clinical study will be used by NewLink in connection with the continued development of HyperAcute immunotherapy and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review of NewLink Genetics. Draft abstracts, manuscripts and materials for presentation at scientific meetings should be provided to the sponsor at least 30 working days prior to abstract or other relevant submission deadlines or as outlined in the clinical trial agreement.

14 APPENDICES

14.1 APPENDIX A: AJCC Staging of Melanoma

AJCC, Cancer Staging Handbook, Seventh Edition

The AJCC staging system is based on three sets of criteria: how thick the tumor is (T), the extent to which it has spread to the lymph nodes (N), and the extent to which it has metastasized to other parts of the body (M). The AJCC staging system is outlined below with the TNM parameters.

Clinical Staging*				**Pathological Staging****			
Stage 0	Tis	N0	M0	**Stage 0**	Tis	N0	M0
Stage IA	T1a	N0	M0	**Stage IA**	T1a	N0	M0
Stage IB	T1b T2a	N0 N0	M0 M0	**Stage IB**	T1b T2a	N0 N0	M0 M0
Stage IIA	T2b T3a	N0 N0	M0 M0	**Stage IIA**	T2b T3a	N0 N0	M0 M0
Stage IIB	T3b T4a	N0 N0	M0 M0	**Stage IIB**	T3b T4a	N0 N0	M0 M0
Stage IIC	T4b	N0	M0	**Stage IIC**	T4b	N0	M0
Stage III	Any T	≥N1	M0	**IIIA**	T1 – 4a T1 – 4a	N1a N2a	M0 M0
				IIIB	T1 – 4b T1 – 4b T1 – 4a T1 – 4a T1 – 4a	N1a N2a N1b N2b N2c	M0 M0 M0 M0 M0
				IIIC	T1 – 4b T1 – 4b T1 – 4b Any T	N1b N2b N2c N3	M0 M0 M0 M0
Stage IV	Any T	Any N	M1	**IV**	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

T classifications:

T classification	Thickness (mm)	Ulceration Status/Mitoses
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	≤ 1.0	a: without ulceration and mitosis < 1/mm^2 b: with ulceration or mitoses ≥ 1/mm^2
T2	1.01 – 2.0	a: without ulceration b: with ulceration
T3	2.01 – 4.0	a: without ulceration b: with ulceration
T4	> 4.0	a: without ulceration b: with ulceration

N Classifications:

N classification	Number of Metastatic Nodes	Nodal Metastatic Mass
NX	Regional nodes cannot be assessed	
N0	No regional metastases detected	
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2 – 3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

M Classifications:

M classification	Site	Serum LDH
M0	No detectable evidence of distant metastases	
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

14.2 APPENDIX B: ECOG Performance Status Criteria.†

ECOG Performance	Description
0	Fully active and able to carry on all pre-disease activities 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 housework, office work, etc.
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.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. (1982) *Am J Clin Oncol* 5:649-655.