NLG-0304: A Phase 2b Study of Ipilimumab With or Without Dorgenmeltucel-L (HyperAcute™ Melanoma) Immunotherapy for Patients With Stage IV Melanoma

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TPS9115

INTRODUCTION

Dorgenmeltucel-L immunotherapy, or HyperAcute Melanoma (HAM), consists of allogeneic melanoma cells that have been genetically modified to express the carbohydrate α(1,3)Gal, to which humans have an inherent pre-existing immunity.

αGal is primarily responsible for the hyperacute rejection of foreign tissue that comprises a potent immune defense mechanism in humans. Dorgenmeltucel-L leverages this mechanism of hyperacute rejection to educate the immune system towards components of the patients' own tumor cells.

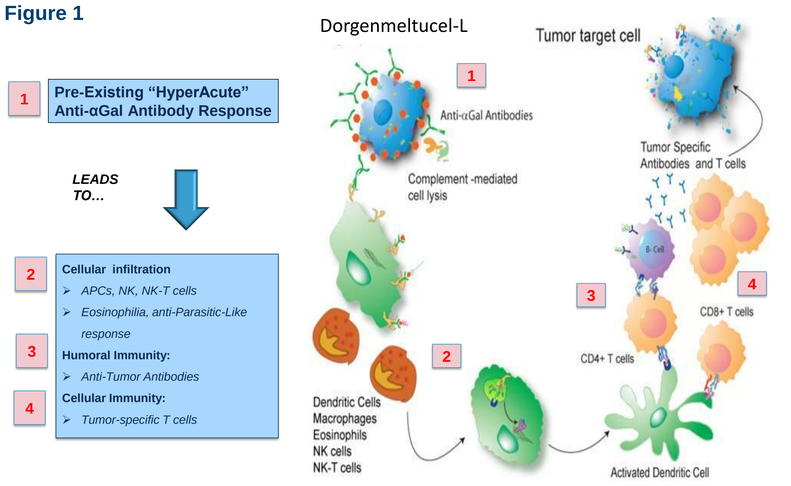
In prior phase 1 and 2 studies, dorgenmeltucel-L has shown a favorable safety profile with no grade 3 or higher immunotherapy related adverse events. In the phase 2 study in combination with pegylated interferon, all evaluable patients developed autoimmune antibodies and 4 developed vitiligo which correlated with either CR or long term recurrence-free survival[1].

Ipilimumab, an anti-CTLA-4 antibody, has now become standard therapy for advanced melanoma patients, particularly those that are BRAF negative. Preclinical data has demonstrated synergy between therapeutic vaccination and anti-CTLA-4 therapy.

This phase 2b study is designed to determine if there is benefit to adding dorgenmeltucel-L to standard ipilimumab therapy. Patients randomized to the combined treatment arm will receive HyperAcute Melanoma immunotherapy as well as ipilimumab. This study regimen is an immunization strategy that attempts to combine two complementary mechanisms that enable and activate the immune system to destroy cancer cells.

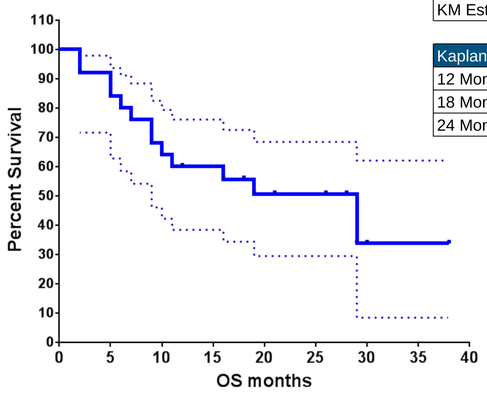
HYPERACUTE THERAPY

Figure 1



PRIOR CLINICAL EXPERIENCE

Figure 2. Kaplan-Meier Survival analysis



Overall Survival (months)	
KM Estimator	29

Kaplan-Meier Survival	
12 Month Survival	60.0 %
18 Month Survival	55.7 %
24 Month Survival	50.6 %

A phase 2 clinical trial (N = 25) evaluated the efficacy of a combination of immunostimulatory agents, the HyperAcute Melanoma Immunotherapy and pegylated interferon α-2b , in patients with refractory, recurrent or metastatic (Stage IV) melanoma (1). A 12-week regimen was conducted with the initial 4 weekly treatments consisting of HAM alone (intradermally) followed by 8 additional treatments of HAM + pegylated interferon α-2b (subcutaneously, 6 µg/kg).

Results showed:

- 7 patients remain disease free, 2 complete responses (1 with regression of multiple metastases) , 1 SD, 2 PD, 13 DOD
- All patients evaluable (21/21) seroconverted to auto-antibodies (anti-cardiolipin, anti-thyroglobulin, or both)
- 4/25 patients developed vitiligo (2 complete tumor regression after completing the trial)
- Anti-α Ab increase after immunization to persistently elevated levels for >200 days in majority of patients

HYPERACUTE MELANOMA

Figure 3.

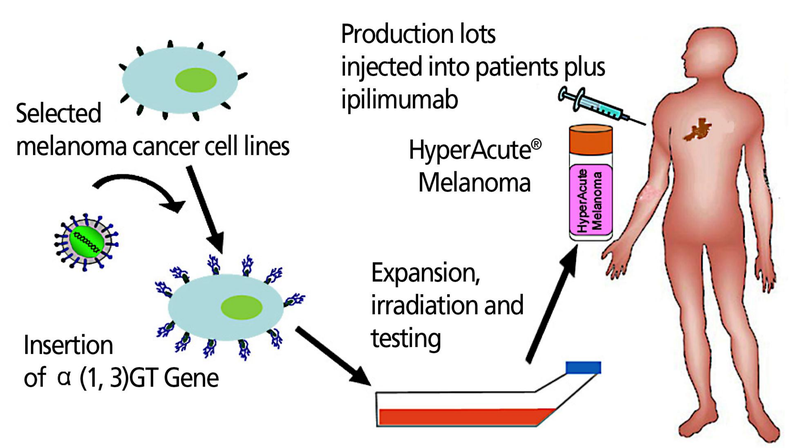


Figure 3. HyperAcute Melanoma Immunotherapy.

HAM Immunotherapy is comprised of three human melanoma cancer cell lines transduced with a a recombinant Moloney murine leukemia virus (MoMLV)-based retroviral vector expressing the murine **α**(1,3)GT gene (HAM1, HAM2 and HAM3). Product is irradiated for safety and administered as a series of intradermal injections.

STUDY OVERVIEW

Patients with advanced stage melanoma are randomized to receive either ipilimumab alone or ipilimumab in combination with dorgenmeltucel-L.

100 total, Randomized 1:1, 50 patients in Arm 1 and 50 patients in Arm 2

Eligibility

- Histological/cytological diagnosis of melanoma
- AJCC Stage IV (any T, any N, M1), metastatic, progressive, refractory, melanoma
- ECOG Performance Status <1
- 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 anti-CTLA4 antibodies is NOT allowed.

Primary Objectives

- Safety of ipilimumab +/- dorgenmltucel-L immunotherapy
- Clinical response rate

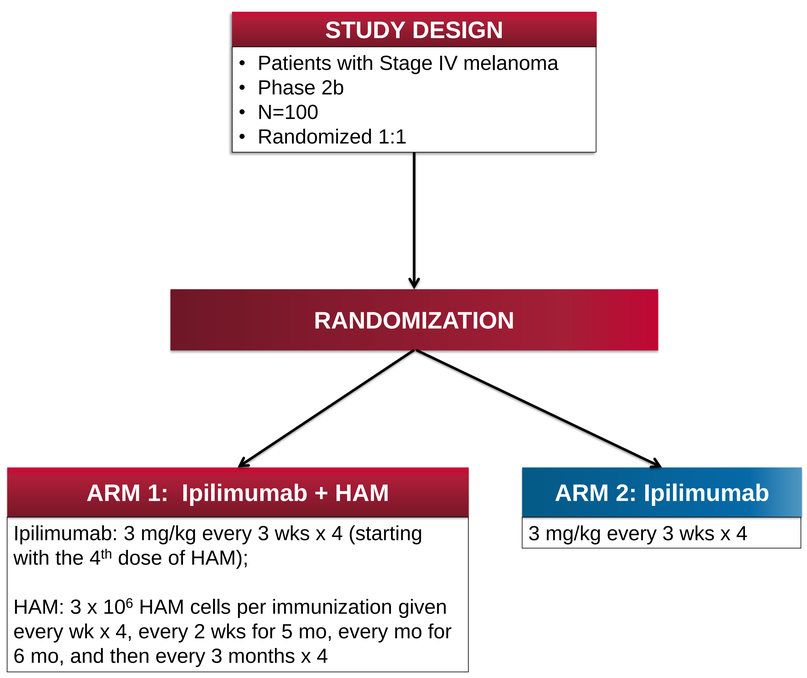
Secondary Objectives

- Disease-free survival
- Progression-free survival
- Overall survival
- Duration of overall response
- Duration of complete response
- Duration of stable disease
- Biologic activity: anti-tumor immune responses in melanoma metastases in responding and non-responding patients; activation of humoral and cellular mediated arms of the host immune system secondary to HAM combined with ipilimumab

Correlative studies

- Patient blood samples are analyzed to determine the mechanism of any observed anti-tumor effect

STUDY SCHEMA



SUMMARY

- In the United States, melanoma is the fifth most common cancer in men and the seventh in women. Locally confined, fully resectable disease may be curable with current therapy, but Stage IV metastatic disease (or relapsed/recurrent disease) is highly refractory to therapy
- Dorgenmeltucel-L (HyperAcute Melanoma) cellular immunotherapy uses a novel approach by inducing hyperacute rejection of immunotherapy cells that may lead to immunity against the patient's melanoma cells.
- A prior clinical study showed that combinatorial immunotherapy with HAM plus pegylated interferon α-2b provided clinical efficacy with tumor regression and concomitant immune activation
- While the anti-CTLA-4 antibody ipilimumab has become a new standard of care for advanced stage melanoma, combining it with HAM may lead to improved immune responses against tumor cells, including potential improvements in survival.
- This phase 2b study compares HAM plus ipilimumab with ipilimumab alone in stage IV melanoma patients

REFERENCES

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CLINICAL TRIALS IDENTIFIER

Clinicaltrials.gov identifier: NCT02054520

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50th American Society of Clinical Oncology Annual Meeting; May 30-June 3, 2014; Chicago, IL