BMT News

NORTHSIDE HOSPITAL CANCER INSTITUTE
BLOOD & MARROW TRANSPLANT PROGRAM

SUMMER 2017 ISSUE

In This Issue:

Ongoing Clinical Trial Evaluating the Use of Bispecific T-Cell Engaging Antibodies for Targeting CD123 Expressing Cancer Cells

Acute myeloid leukemia (AML) is among the most common hematologic cancers. AML typically has a bimodal incidence, with peaks occurring in early childhood and in late adulthood. However, all age groups are affected. Multi-agent chemotherapy has represented the standard of care for treatment of AML for more than forty years. It is now widely recognized that AML is heterogeneous. While approximately 75% of the patients treated with standard chemotherapy will achieve a complete remission (CR), only a small fraction of subtypes have a high likelihood of cure with chemotherapy alone.[1] Furthermore, aggressive chemotherapy can be poorly tolerated in elderly patients who comprise a significant proportion of AML patients. Once relapse occurs, chemotherapy is typically ineffective as a cure and allogeneic hematopoietic transplant is the only known curative therapy in this setting. Unfortunately, the efficacy of allogeneic transplantation is also limited by the potential for disease relapse and toxicity.

Antibody-based therapy which targets cell-surface proteins expressed on malignant cells, has radically impacted the outcome of other cancers such as B-cell non-Hodgkin lymphoma. In AML, antibody-based therapies targeting the CD33 antigen have so far not significantly impacted prognosis. The interleukin receptor alpha chain (CD123) is an antigen that is widely expressed on AML cells. Other malignancies known to express CD123 are B- or T-cell acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), hairy cell leukemia, and blastic plasmacytoid dendritic cell neoplasm (BPDCN). CD123 expression on malignancies is associated with higher proliferative rates, increased resistance to apoptosis induced by growth factor deprivation, increased cellularity at diagnosis, and a poorer prognosis.[2] Thus, targeting the CD123 antigen represents a promising strategy against such malignancies. XmAb®14045 is a CD123 targeting bispecific T-cell engaging antibody.[3]

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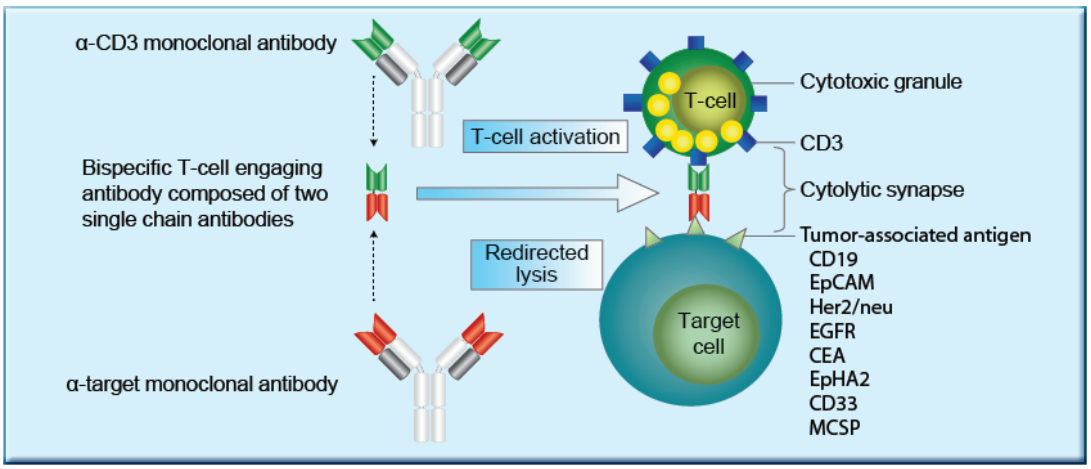


Clinical Trial Updates

Novel Acute Myeloid Leukemia Immunotherapy BMT Clinical Trial Open to Enrollment: Lymphodepletion and Pembrolizumab in High-Risk AML Patients Not Eligible for Allogeneic Stem Cell Transplantation

With support from Merck, the NSH BMT program is enrolling high-risk acute myeloid leukemia (AML) patients who are not eligible for allogeneic transplant onto this cutting-edge immunotherapy clinical research trial. AML is the most common acute leukemia in adults. Some patients with AML are not candidates for allogeneic transplantation due to age, overall health, psychosocial factors, and/or lack of an available donor. This study is designed to stimulate anti-leukemic immunity within the host in order to promote immune-mediated elimination of AML and hopefully break immune tolerance to AML cells to provide better outcomes in patients with non-favorable risk AML.

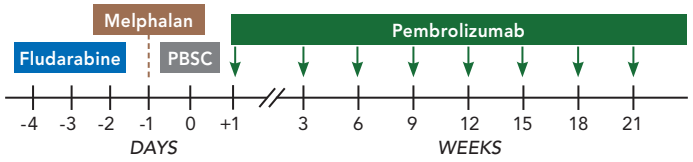
NSH 1150 is a phase II, single-center trial enrolling 20 patients diagnosed with AML over a 36-month period. Patients will begin lymphodepleting chemotherapy on D-4 and receive an autologous transplant on D0. Patients will receive a total of 8 doses of Pembrolizumab over 24 weeks beginning on Day +1 and will be followed for 2 years post-transplant.

OBJECTIVES

Primary: to estimate the 2-year relapse risk

Secondary: to assess the safety of Pembrolizumab in patients with AML following lymphodepleting chemotherapy

TREATMENT & FOLLOW-UP



Fludarabine: 30 mg/m^2/d x 3 days (D-4 to -2)
Melphalan: 180 mg/m^2 (ages 18-60) or 140mg/m^2 (ages 61-75) (D-1)
Pembrolizumab: 200 mg/dose Q3 weeks x 8 doses beginning D+1

SPECIAL CONSIDERATIONS

See Table 2 in the protocol for Pembrolizumab dose modifications

- Chemotherapy dosing:
  - To be based on ideal body weight for patients who weigh 100-130% of IBW
  - To be based on actual body weight for patients who weigh less than 100% of IBW
- Research samples required at BMBx collection
- Bone marrow biopsies optional but recommended at 1 and 2 months post-transplant in addition to standard disease assessment timepoints

If you have any questions, would like to discuss study logistics, or the eligibility of any patients, please contact Stacey Brown, NSH BMT/Leukemia Clinical Research Manager, at **404-851-8238** or **stacey.brown@northside.com**

PEMBROLIZUMAB SIDE EFFECTS

Common: pruritus, fatigue, decreased appetite, shortness of breath, cough, joint pain, fever, lower-extremity edema, weakness, back pain, rash, hyponatremia, stomach pain, nausea, diarrhea, vomiting, anemia, skin color loss

Serious: lung inflammation, joint pain, bowel/gut inflammation (see protocol for full list of side effects and risk profile)

ELIGIBILITY CRITERIA

Inclusion Criteria:

- 18-78 years of age
- Non-favorable risk AML
  - Poor risk cytogenetics
  - Intermediate-risk cytogenetics with non-favorable molecular testing
  - CBF AML associated with C-kit mutation
- Completed 1 cycle of consolidation chemo with no residual disease by morphology, flow, cytogenetics or FISH
- In CR1 or subsequent CR
- Collection of at least 2x10^6/kg CD34+ cells
- Adequate lab values

Exclusion Criteria:

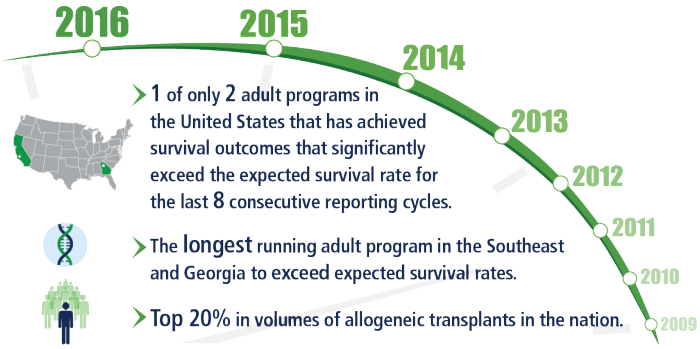
- Not eligible for an allogeneic stem cell transplant
- Received investigational agents within 4 weeks of first dose
- Prior chemo or radiation therapy within 2 weeks of first dose
- Uncontrolled infection
- History of active TB
- Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
- Received live vaccine within 30 days of first dose

• Regional and National Recognition •

Over-Performing 2009—2016: Survival Outcome Rates in Allogeneic Transplants

The NSH BMT Program is the only adult BMT Program in Georgia to achieve survival outcomes that significantly exceeded the expected survival rate for allogeneic transplants for the last 8 consecutive reporting cycles (2009-2016).[1,2] Over the past eight years, we believe our programs' commitment to quality has consistently increased patient survival rates. There were 179 adult and pediatric transplant centers included in the analysis.

Exceeding Survival Rates in Allogeneic Transplant



Dedicated to Clinical Excellence & Remarkable Patient Satisfaction

- Allogeneic one year survival outcomes that are among the best in the nation.
- Physicians available 24 hours/7 days a week.
- Inpatient and outpatient transplant program.
- Dedicated specialty trained clinical team.
- Survivorship events.
- Satisfaction survey results consistently above the 90th percentile for physician care, nursing care and overall hospital experience.[3]

For more information, please visit
https://bethematch.org/tcdirectory/index/60

1. Reported outcome data from bethematch.org. This survival information includes only patients who received their first allogeneic transplant between January 1, 2012 and December 31, 2014 using unrelated or related donors, and who had reported follow-up;
2. Final 2016 Transplant Center Specific Survival Report, December 12, 2016.
3. According to the 2016 Press Ganey HCAHPS Regulatory Survey.

NSH BMT Program Presents at 58th Annual American Society of Hematology (ASH) and 2017 American Society of Blood and Marrow Transplant (ASBMT) BMT Tandem Meetings

The NSH BMT Program physicians and clinical research team have again been recognized by the American Society of Hematology (ASH) and American Society of Blood and Marrow Transplant (ASBMT) for their commitment to participate in state-of-the-art blood and marrow transplant clinical research trials. Having access to cutting-edge clinical research trials allows our patients to receive the most innovative treatments available without travelling to a major academic center.


BMTGA Physicians


NSH-BMT/Leukemia Program Clinical Research Team

2016 ASH Oral Presentations

1. Current graft-versus-host-disease (GVHD), relapse-free survival – a novel, dynamic composite endpoint to better define effectiveness following allogeneic hematopoietic cell transplantation. Solomon S, Sizemore C, Ridgeway M, Zhang X, **Solh M**, **Morris LE**, **Holland HK**, **Bashey A**. ORAL ABSTRACT # 1170
2. Myeloablative allogeneic hematopoietic cell transplantation performed without routine inpatient admission: a single center experience of 462 consecutive patients. **Bashey A**, Zhang X, Brown S, Jackson K, **Solh M**, **Lawrence M**, **Holland HK, Solomon S**. ORAL ABSTRACT # 661
3. Comparison of peripheral blood stem cells (PBSC) to bone marrow (BM) for T-replete HLA-Haploidentical donor transplantation using post-transplant cyclophosphamide. **Bashey A**, Zhang M, Mccurdy S, Ciurea S, St. Martin A, Anasetti C, Argall T, Fasan O, Gaballa S, Hamandani M, Malki M, Munshi P, Nakamura R, O'Donnell P, Perales M, Raj K, Rocha V, Romee R, Rowley S, Salit R, **Solh M**, Soiffer R, Wingard J, Weisdorf D, Horowitz M, Fuchs E, Eapen M. ORAL ABSTRACT # 683

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Regional and National Recognition

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NSH BMT Program Presents at 58th Annual American Society of Hematology (ASH) and 2017 American Society of Blood and Marrow Transplant (ASBMT) BMT Tandem Meetings

2017 ASBMT BMT Tandem Meetings Oral Presentations

1. **Sanacore M**, Eaton S, **Morris LE**, **Solomon S**, **Bashey A**, **Solh M**, **Holland HK**. Prospective assessment of diagnostic infectious disease molecular PCR testing with early fiber-optic bronchoscopy (FOB) in the evaluation of new pulmonary infiltrates in hematopoietic stem cell transplantation (HSCT) and acute leukemia (AL) patients (pts). ORAL ABSTRACT # 9355
2. **Solh M**, **Dickhaus E**, Gruber L, **Bashey A**, **Solomon S**, **Holland HK**, **Morris LE**, Brown S. Fevers post infusion of T-cell replete HLA mismatched haploidentical hematopoietic stem cells. ORAL ABSTRACT # 8901

(continued from page 1)

Ongoing Clinical Trial Evaluating the Use of Bispecific T-Cell Engaging Antibodies for Targeting CD123 Expressing Cancer Cells

Bispecific antibodies allow for simultaneous binding of two different antigens. This unique approach allows for binding to an antigen on the cancer cell and to the T-cell surface glycoproteins activating the innate immune system. XmAb®14045 is a humanized bsAb that binds both CD3 and the tumor antigen CD123, allowing for recruitment of cytotoxic T-cells to kill CD123+ tumor cells. More specifically, T-cell redirecting bispecific antibodies are full-length immunoglobulin molecules that introduce T-cells to the tumor cells. Activation only occurs when both binding sites are occupied.[3] Redirecting and activating T-cells by engaging CD3 may lead to more potent immune killing of cancer cells compared to monospecific antibodies, such as rituximab or trastuzumab.[4]

The NSH Leukemia program is excited to be collaborating with Xencor on a multicenter, open-label, multi-dose phase 1 dose-escalation study of XmAb®14045 in patients with AML and other tumor types reported to express CD123. Eligible patients must have relapsed or refractory disease after standard therapy.

This is a first-in-humans study of this novel targeted therapeutic bispecific T-cell engaging antibody designed to determine optimal dose and preliminary efficacy. Unlike smaller bispecific T-cell engaging antibody molecules like the FDA-approved, CD19 targeting molecule blinatumumab (Amgen), XmAb®1045 has a long half-life in humans and does not have to be administered by continuous infusion. Data from pre-clinical studies, in both primates and mice, strongly suggest activity against human AML, with a high probability of activity against other CD123 expressing neoplasms.

Select inclusion criteria for NSH 1164 include patients who are 18 years of age or older with primary or secondary AML (including erythroleukemia and eosinophilic leukemia, but excluding acute promyelocytic leukemia), B-cell ALL, BPDCN, CML (in blast phase, resistant or intolerant to tyrosine kinase inhibitor therapy). Patients with relapsed or refractory disease with no available standard therapy are also eligible. For AML, this includes patients with:

a. newly diagnosed leukemia refractory to ≥2 induction attempts,
b. leukemia in first relapse with initial CR duration of <6 months,
c. leukemia in first relapse following ≥1 unsuccessful salvage attempts, or
d. leukemia in second or higher relapse.

For further information regarding this trial, please contact Stacey Brown at:
stacey.brown@northside.com or **(404) 851-8238**.

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med.* 2015;373(12):1136–52.
2. Fan D, Li Z, Zhang X, et al. AntiCD3Fv fused to human interleukin-3 deletion variant redirected T cells against human acute myeloid leukemic stem cells. *J Hematol Oncol.* 2015;8(1):18.
3. Smits NC and Sentman CL. Bispecific T-Cell Engagers (BiTEs) as Treatment of B-Cell Lymphoma. *Journal of Clinical Oncology.* 2016;34:10:1131–1133.
4. Kontermann RE. Dual targeting strategies with bispecific antibodies. *MAbs.* 2012;4:182–197.

Open Clinical Trials

BMT

NSH 1074: A Phase II Trial of Nonmyeloablative Haploidentical Peripheral Blood Stem Cell Transplantation Followed by Maintenance Therapy With the Novel Oral Proteasome Inhibitor, MLN9708, in Patient With High-Risk Hematologic Malignancies

NSH 1107: A Phase II Trial of High-Dose Bendamustine, Etoposide, Cytarabine, and Melphalan (BeEAM) in the Up-Front Treatment of Multiple Myeloma

NSH 1108: BMT-CTN-1301 – A Randomized, Multicenter Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft Versus Host-Disease

NSH 1125: A Multicenter Phase II, Double-Blind Placebo Controlled Trial of Maintenance Ixazomib After Allogeneic Hematopoietic Stem Cell Transplantation for High-Risk Multiple Myeloma BMT CTN 1302

NSH 1132: A Phase II Trial of Reduced Intensity Conditioning and Transplantation of Partially HLA-Mismatched Peripheral Blood Stem Cells for Patients With Hematologic Malignancies

NSH 1148: A Randomized Phase II Study of Autologous Stem Cell Transplantation With Tadalafil and Lenalidomide Maintenance With or Without Activated Marrow Infiltrating Lymphocytes (MILs) in High-Risk Myeloma

NSH 1150: Phase II Trial of Lymphodepletion and Anti-PD-1 Blockade to Reduce Relapse in High-Risk AML Patients Who Are Not Eligible for Allogeneic Stem Cell Transplantation

NSH 1156: BMT-CTN-1501 – A Randomized, Phase 2, Multicenter, Open-Label Study Comparing Sirolimus to Prednisone in Patients With Minnesota Standard Risk, Ann Arbor 1 / 2 Confirmed Acute GVHD

NSH 1158: A Study of T-Cell Replete, HLA-Mismatched Haploidentical Bone Marrow Transplantation With Post-Transplant Cyclophosphamide as a Front-Line Therapy for Patients With Severe Aplastic Anemia Lacking HLA-Matched Related Donor

NSH 1173: A Phase II Study Evaluating the Safety and Efficacy of BL-8040 for the Mobilization of Donor Hematopoietic Stem Cells and Allogeneic Transplantation in Patients With Advanced Hematological Malignancies

NSH 1175: BMT-CTN-1502 – Optimizing Cord Blood and Haploidentical Aplastic Anemia Transplantation (CHAMP)

Leukemia/Lymphoma/Multiple Myeloma

NSH 1032: A Phase I/Ib Study of Ipilimumab or Nivolumab in Patients With Relapsed Hematologic Malignancies After Allogeneic Hematopoietic Cell Transplantation

NSH 1095: Collection of Bone Marrow and Peripheral Blood (PB) Samples from Patients With Leukemia and PB from the BM Donors (BMD) to Identify Leukemia-Specific Antigens (LSA) and Graft Versus Host Disease Antigens (GVHDA) for Use in Cellular Immunotherapy

NSH 1099: E1910 – Phase 3 Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL Negative B-ALL in Adults

NSH 1115: A Multicenter Phase I/Ib Study Evaluating the Efficacy and Safety of the Novel PI3k Delta Inhibitor TGR-1202 in Combination With Ibrutinib in Patients With Select B-Cell Malignancies

NSH 1137: Expanded Access Protocol of CPX-351 (Cytarabine: Daunorubicin) Liposome for Injection for Patients 60-75 Years of Age With Secondary AML

NSH 1144: A Phase 2, Randomized, Biomarker-Driven, Clinical Study in Patients With Relapsed/Refractory AML With an Exploratory Arm in Patients With Newly Diagnosed High-Risk AML

NSH 1164: A Phase 1 Multiple Dose Study to Evaluate the Safety and Tolerability of XmAb®14045 in Patients With CD123-Expressing Hematological Malignancies

NSH 1165: Phase 1 Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients With Relapsed or Refractory B-Cell Lineage Non Hodgkin Lymphoma (B-NHL)

NSH 1169: A Phase I/II Study of SEL24 in Patients With Acute Myeloid Leukemia

C-203: Gemtuzumab Ozogamicin (Mylotarg®) Expanded Access Protocol for Treatment of Patients in the United States With Relapsed/Refractory Acute Myelogenous Leukemia Who May Benefit From Treatment and Have No Access to Other Comparable/Alternative Therapy

C-250: A Phase 1, Open-Label, Dose-Escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients With Relapsed or Refractory CD25-Positive Acute Myeloid Leukemia (AML)

C-262: A Phase 3, Open-label, Multicenter, Randomized Study of ASP2215 Versus Salvage Chemotherapy in Patients With Relapsed or Refractory AML With FLT3 Mutation

Supportive Care

NSH 721: NMDP Recipient Consent for Participation in Registry, Research Database, and Research Sample Repository

NSH 943: A Multicenter Access and Distribution Protocol for Unlicensed Cryopreserved Cord Blood Units (CBUs) for Transplantation in Pediatric and Adult Patients With Hematologic Malignancies and Other Indications

NSH 995: A Multicenter Safety Study of Unlicensed, Investigational Cryopreserved Cord Blood Units (CBUs) Manufactured by the National Cord Blood Program (NCBP) and Provided for Unrelated Hematopoietic Stem Cell Transplantation of Pediatric and Adult Patients

NSH 1113: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Multicenter Study Evaluating Antiviral Effects, Pharmacokinetics, Safety, and Tolerability of GS-5806 in HCT Recipients With Respiratory Syncytial Virus (RSV) Infection of the Upper Respiratory Tract

Community Engagement

NSH BMT Program Survivor Reunion

Georgia Aquarium, October 22, 2016

On October 22, 2016, the NSH BMT Program held its survivor reunion at The Georgia Aquarium. Over 500 attendees, including patients, donors, caregivers, and family members participated in this inspirational and festive occasion. We would like to thank the many volunteers who spent hours of their time organizing this special event.

Left: Neal Brasfield, unrelated allogeneic transplant patient, meets his donor at the Georgia Aquarium reunion.

The Stovall Foundation Donates Apartments to the NSH BMT Program

Since 2003, The Stovall Foundation, led by Ray and Martha Stovall, provides local lodging for transplant patients and their caregivers. The Stovall Foundation raises funds, provides ongoing management, and supports operations for a total of nine corporate apartments. The Stovall Foundation's generous donations have allowed patients and their family members, who live 50 miles or greater from NSH, to be able to stay at a comfortable, high quality, safe and clean facility at no cost. All apartments are fully furnished and are located conveniently to Northside Hospital.

The Stovalls' deep commitment to community and making a difference in the lives of transplant patients and their family members has allowed our program to treat patients who may not have had the funds to travel to our program to receive lifesaving cancer treatment. Martha states, 'Our son Kenneth had his transplant care at Northside, and we understand the many challenges treatment creates for the patient and family. We hope our apartment donations can bring comfort and solace to those families who are experiencing health and life challenges.' We thank the Stovalls for their long-standing support of our program.

For more information about the Stovall Foundation, please email **stovallrm@windstream.net**

Martha Stovall, Dr. Scott Solomon, Ray Stovall

Community Engagement

2017 Annual Northside Hospital Charity Golf Classic Raised Funds to Support Cancer Research and NSH BMT Program

On May 15, 2017, NSH BMT's primary fundraiser, the NSH Charity Golf Classic, was held at the Atlanta Athletic Club. Under the direction of the NSH Foundation, this annual event assists patients with local lodging, transportation and other services.

We thank the NSH Foundation for their tireless efforts in organizing and coordinating this annual fundraising event.

Dr. Asad Bashey, MD, PhD, Presented at the Annual Georgia Leukemia and Lymphoma Society (LLS) Blood Cancer Conference

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The Blood & Marrow Transplant Group
OF GEORGIA

NORTHSIDE HOSPITAL
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