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The Blood and Marrow Transplant Program at Northside Hospital News

New Clinical Trial Assesses Use of CTLA-4 Blockade with Ipilimumab

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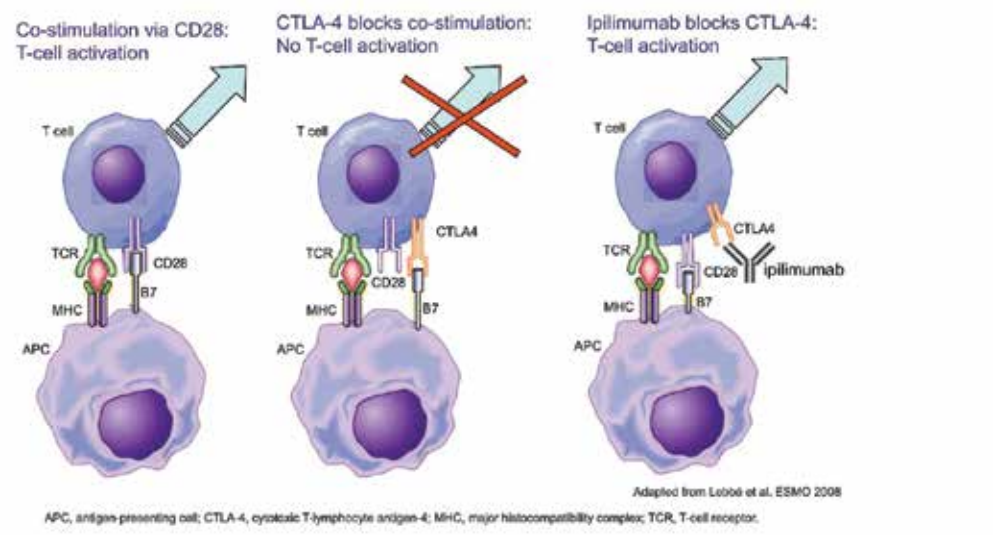
Ipilimumab Blocks Inhibition of Co-Stimulation by CTLA-4



Allogeneic hematopoietic stem cell transplantation (alloSCT) can cure several hematological malignancies that are otherwise incurable using chemotherapy alone. Adoptive immunotherapy in the form of a donor T-cell mediated graft-vs.-tumor (GVT) effect is felt to be the most important curative component of allo-SCT. However, suboptimal stimulation of donor T cells following allo-SCT may prevent the development of this effect and ultimately lead to disease relapse and treatment failure. Relapse of malignancy post-allo-SCT is usually associated with a very poor outcome. Although conventional therapy can induce responses in this setting, the responses are typically not durable. Additional infusion of donor-derived lymphocytes (Donor Lymphocyte Infusion, DLI) is commonly used to enhance GVT following relapse. However, while highly effective in patients with some selected malignancies (e.g. molecular relapse of chronic myelogenous leukemia), efficacy in other hematologic malignancies is modest. Furthermore, DLI can induce potentially life-threatening graft-versus-host disease (GVHD) in these patients. Thus, there exists a significant need for other strategies that augment the GVT effect thus enabling immunological eradication of malignancy in patients who relapse post allo-SCT.

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Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an important negative regulator of antigen-stimulated T-cell activation and proliferation. CTLA-4 is expressed on T-cells and its expression is upregulated following antigen-stimulated T-cell activation. CTLA4 counteracts the activity of the co-stimulatory T-cell receptor CD28 by out-competing it for its ligands CD80 (B7-1) and CD86 (B7-2) which are expressed on antigen presenting cells. CTLA4 has a much higher affinity for these ligands than CD28. Binding of CTLA4 to its ligands leads to negative co-stimulatory signaling as well as sequestration of the ligands. Ipilimumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that antagonizes CTLA4. Upon binding to CTLA-4, ipilimumab blocks the interaction of CTLA-4 with its ligands leading to augmented T-cell activation.

Ipilimumab has been studied in over 4000 subjects in several cancer types but the clinical focus to date has been melanoma, prostate cancer, and lung cancer. The drug is being investigated as monotherapy and in combination with chemotherapy, radiation, and other immunotherapy. It is currently FDA approved for unresectable or metastatic melanoma. The main toxicity observed has been organ-specific immune adverse events (IAE).

Preliminary studies evaluating ipilimumab in the setting of hematologic malignancies have recently completed or are currently underway. Ansell and colleagues conducted a phase I study of 18 patients with relapsed/refractory NHL to evaluate the safety, immunologic activity, and potential clinical efficacy of ipilimumab.[1] Ipilimumab was given as a single dose of 3mg/kg, then 1mg/kg monthly for 3 months with escalation to 3mg/kg monthly for 4 months. The drug was well tolerated at the doses used. Two patients experienced a clinical response (CR). One patient had an ongoing CR of greater than 31 months and one had a partial response (PR) lasting 19 months. T cell proliferation to recall antigens was >2 fold after ipilimumab therapy in 5 of 15 cases.

Ipilimumab and other biological agents that can suppress barriers to antigen-induced T-cell activation also have the potential to stimulate GVT effects following allo-SCT. However, they have not yet been extensively studied within this context. Furthermore, they theoretically have the potential to induce GVHD.

An initial study conducted by our group enrolled 29 patients with recurrent or progressive malignancies following allo-SCT. Patients received a single infusion at dose cohorts between 0.1 and 3 mg/kg. The study found that ipilimumab was well tolerated at doses up to 3 mg/kg.[2] Dose limiting toxicity (DLT) did not occur. Immune adverse events (IAE) were seen in 4 patients and consisted of grade 3 arthritis, grade 2 hyperthyroidism, and grade 4 pneumonitis responsive to corticosteroids. Complete remission was documented in 2 patients with Hodgkin lymphoma and objective partial remission with regression of bulky adenopathy at multiple sites was observed 1 patient with highly refractory mantle cell lymphoma. Importantly, ipilimumab did not induce GVHD or graft rejection in this study. Zhou and colleagues studied immunophenotypes of peripheral blood T cells in these patients before and after the impilimumab dose and found increased CD4+, CD4+HLA-DR+T lymphocyte counts and intracellular CTLA-4 expression at the 3 mg/kg dose level.[3] Treg cell numbers did not significantly change.

These trials demonstrate the potential for patients with relapsed hematologic malignancies following allo-SCT to respond to ipilimumab without DLT or worsened GVHD. However, the highest dose used was 3mg/kg and it is possible that even higher doses may also be well tolerated with greater efficacy. Melanoma patients, for example, experience a three-fold increase in efficacy with a dose of 10mg/kg compared to 3 mg/kg.[4] Thus, there exists a need for the evaluation of doses higher than 3mg/kg and the use of multiple/repeated dosing of ipilimumab in patients with relapse of malignancy post- allo-SCT.

NSH 1032 is a new phase Ib study assessing the efficiacy and safety of ipilimumab in patients with hematologic malignancies that have relapsed post-allo SCT. This will provide a novel option for patients with disease relapse following allo-SCT who would otherwise be expected to have a very poor prognosis. The phase I portion will evaluate multiple dosage tiers of the drug up to 10mg/kg using a multiple dosing regimen, to determine the maximum tolerated dose in this patient population. Following this, an expansion cohort will be treated at the maximum tolerated dose to better characterize the toxicity profile of the drug and to obtain efficacy data. Laboratory correlates will look at both phenotypic and functional changes caused by ipilimumab in a wide variety of immune cells, including T cells, B cells, NK cells, and dendritic cells. Cytokine production induced by ipilimumab will also be studied. Eligible patients will be treated within 3 years after withdrawal of all prophylactic immunosuppression and must not have had any immunosuppression, anti-tumor therapy or other investigational agents within 4 weeks prior to registration. Patients who have had a DLI within 8 weeks of registration and patients with autoimmune disease are excluded. Outpatients will receive ipilimumab every 3 weeks for 4 cycles then every 12 weeks of maintenance treatment for up to one year.

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

References:

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2. Bashey A, Medina B, Corringham S, et al. CTLA-4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. Blood. 2009;113:1581-1588.
3. Zhou J, Bashey A, Zhong R, et al. CTLA-4 Blockade following relapse of malignancy after allogeneic stem cell transplantation is associated with T cell activation but not increased levels of T regulatory cells. Biol Blood Marrow Transplant. 2011;17:682-692.
4. Dai D, Wu C, Parker SM et al. Model-based evaluation of ipilimumab dosage regimen in patients with advanced melanoma. J Clin Oncol (Meeting abstracts). 2008; 26 (May 20 supplement)

NSH-BMT, Leukemia & Lymphoma Society and Dana Farber Cancer Institute Collaborate on Innovative Research Partnership

The Leukemia & Lymphoma Society (LLS) and the Dana-Farber Cancer Institute have established a network of sites for clinical trial testing of innovative blood cancer therapies in community oncology settings across the country. This groundbreaking Blood Cancer Research Partnership (BCRP), dana-farber.org/BCRP, will bring clinical trials closer to where patients live and help to address one of the primary bottlenecks in the development of new cancer therapies: the need for more patients to take part in trials. NSH-BMT is one of ten sites who have been selected to participate in this prestigious partnership.

LLS will be investing $1,050,000 in this three-year project. "This novel partnership between Dana-Farber Cancer Institute and LLS supports the mission of both organizations – to bring cutting-edge clinical research to a wider spectrum of patients with blood cancers today in order to change the paradigms of clinical care for patients tomorrow," said Blood Cancer Research Partnership Co-Director Robert Soiffer, M.D., who is the chief of the Division of Hematologic Malignancies at Dana-Farber. "The BCRP consortium will provide the opportunity for the Division of Hematologic Malignancies to extend clinical research trials to patients who are outside our regional area and do not have the capacity to come to Dana-Farber."

For more information about NSH-BMT's affiliation with the Dana-Farber Cancer Institute, please call Stacey Brown, CCRP, Clinical Research & Data Supervisor, at 404-851-8238.

NSH-BMT Among Best in National Survival Outcomes

For the fourth consecutive year, NSH-BMT commitment to quality patient care has resulted in the Program being recognized as one of seven centers out of almost 130 adult transplant programs in the country with survival outcomes that significantly exceed the expected range in related and unrelated allogeneic donor transplants.[1]

The NSH-BMT Program is committed to providing our patients with outstanding clinical care as demonstrated by our patient centered comprehensive quality management program. These efforts have resulted in the Program having one of the BEST one-year survival outcomes for related and unrelated donor transplants as reported on www.marrow.org for the time period of January 1, 2008 - December 31, 2010. The NSH-BMT Program is one of only TWO transplant programs in the U.S., who performed significantly better than their expected range for the past four consecutive reporting cycles.

Center Name	Actual One-Year Survival[1]	Expected Survival Outcomes[2]
Northside Hospital	78%	52-67%
City of Hope	73%	62-68%
Johns Hopkins	73%	63-72%
Memorial Sloan Kettering	73%	57-66%
University of California - SF	72%	55-71%
Roswell Park	70%	51-65%
Karmanos Cancer Center	62%	49-60%

[1] Actual one-year survival. The actual one-year survival rate is based on all patients who received their first allogeneic transplant between January 1, 2008 and December 31, 2010, using unrelated or related donors, and who had at least a 100-day follow-up. This number reflects the percentage of patients at this center who survived one year or more after transplant. The estimated national observed one-year survival was 64.65 percent in the 18,947 patients transplanted in the United States. www.marrow.org

[2] Expected range for one-year survival. The expected range for one-year survival tate is adjusted for the mix of risk factors that can affect patient survival, such as HLA matching, recipient's age, disease and disease stage, and overall health before transplant. The expected range for one-year survival rate shows what the survival would be if the center's same patient population had their transplants at a transplant center with results equal to the national average. www.marrow.org.

- NSH-BMT Program is one of only seven elite programs out of approximately 130 in the United States, and the ONLY program in Georgia and the Southeast, to have one year survival outcomes that exceed expected outcomes for related and unrelated allogeneic donor transplants
- This analysis includes ONLY patients who received their FIRST ALLOGENEIC transplant between January 1, 2008 and December 31, 2010 using unrelated or related donors, and who had at least a 100 day follow-up.
- Center-Specific Analysis is adjusted for the mix of risk factors that can affect patient survival, such as HLA matching, recipient's age, disease and stage, and overall health before transplant.
- For more information please visit www.marrow.org.

Adult Transplant Programs Exceeding Expected Outcomes[1]

[1] Reported outcome data from www.marrow.org. This analysis includes ONLY patients who received their FIRST ALLOGENIC transplant between January 1, 2008 and December 31, 2010 using unrelated or related donors, and who had at least a 100-day follow-up. The analysis considered many recipient-specific factors known to influence transplant survival, such as age, diagnosis, disease stage, general health, etc.

BeTheMatch's Walk-Run Raises Over $80,000.00!

NSH-BMT Program's team participated in the 2013 Be The Match® Walk-Run on June 15, 2013, at Atlantic Station, Central Park. Over $80,000.00 was raised by the Atlanta community to help raise awareness and funds to cure blood cancers. There were 625 individuals who participated in the Walk-Run where:

- 29% of participants had a friend who received a transplant or who was searching for one
- 24% were family members of a transplant recipient or searching patient
- The percentage of family and friend participation was higher than other national BeTheMatch® Annual Walk-Runs

NSH-BMT would like to thank BeTheMatch® for their dedication and efforts to create community awareness and funding to help find a cure for blood cancers.

BE THE MATCH®

New NSH-BMT/Leukemia Clinical Trials Accepting Enrollment

Allogeneic Hematopoietic Cell Transplant for Hematological Cancers and Myelodysplastic Syndromes in HIV-Infected Individuals: NSH IRB 959

Phase II BMT CTN multi-center trial to assess the feasibility and safety of reduced-intensity or fully-ablative allogeneic hematopoietic cell transplantation (HCT) in HIV-infected patients. 15 patients will be transplanted at multiple sites over two years. Where feasible, an attempt will be made to identify HLA-compatible hematopoietic stem cell donors who are homozygotes for the delta32 mutation of the chemokine receptor 5 (CCR5delta32). Patients will undergo a treatment plan review prior to registration on the trial. All patients will undergo allogeneic HCT from a matched sibling or unrelated donor. The physician will choose the regimen. This study is sponsored by NIH & BMT CTN.

An Open-Label, Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigator's Choice in Adult Patients with Relapsed or Refractory $CD22^{+}$ Acute Lymphoblastic Leukemia (ALL): NSH IRB 1011

An open label, multi-center randomized (1:1) phase III study in patients with relapsed or refractory $CD22^{+}$ ALL to determine the efficacy (defined as CR/CRi) of inotuzumab ozogamicin (Arm A) versus the investigator's choice of chemotherapy (Arm B). At least 194 patients are expected to be randomized over approximately 26 months. The trial is sponsored by Pfizer and inotuzumab ozogamicin will be provided to the site.

For more information, please call Stacey Brown, CCRP, Clinical Research & Data Supervisor at 404-851-8238.

2013 Annual NSH Golf Tournament Raises Record Amount for NSH-BMT Program

On May 20, 2012, NSH-BMT's primary fundraiser, the 2013 Annual NSH Golf Tournament, was held at the Atlanta Athletic Club. The event was a great success. The 2013 tournament, which brought in a record number of attendees and sponsors, raised a generous sum of money for the NSH-BMT Program. The Northside Hospital's Charity Golf Tournament provides many financial services to the NSH-BMT patient and their families.

In 2012, over $150,000.00 in Golf Tournament contributions assisted patients with:

- Local lodging assistance
- Transportation services
- Outpatient pharmacy financial assistance
- Medical financial assistance

Without these additional resources, many patients would not be able to undergo a lifesaving transplant. We thank the NSH Foundation for their tireless efforts in organizing and coordinating this life-changing annual event.

NSH-BMT Program Nominee for Atlanta Magazine's 2013 GroundBreaker of the Year Award

Atlanta Magazine has selected NSH-BMT as one of 2013's GroundBreaker of the year nominees. NSH-BMT Program and our patient, Bill Kahler, are featured in Atlanta Magazine's November GroundBreaker edition. Bill underwent a haploidentical (half tissue match) allogeneic transplant where his son served as his donor. In collaboration with Johns Hopkins University's Blood and Marrow Transplant Program, NSH-BMT has been a national leader in providing haploidentical transplants to those patients who do not have a full match related or unrelated allogeneic donor. NSH-BMT has organized their program to focus on factors that continuously produce outstanding survival outcomes, clinical research and quality.

Atlanta MAGAZINE GROUNDBREAKER AWARDS

A Celebration of Life: NSH-BMT Hosts Survivor Reunion at The Fernbank Museum

On October 19, 2013, approximately five hundred guests, which included over 150 patients, their caregivers and the NSH-BMT Program staff came to the Fernbank Museum to celebrate their survivorship and life. Guests were inspired by the key note address given by our patient Alyssa Phillips. Alyssa spoke of her journey from being a patient to leading a life of wellness. Patients were recognized for their years into survivorship, including the very first patient transplanted at NSH-BMT over 15 years ago. Ray and Martha Stovall, of the Stovall Hope Foundation, were honored with an award recognizing their years of service to NSH-BMT patients and families. The Stovall Hope Foundation allows patients and their caregivers to stay in comfortable, spacious and cost free living quarters while undergoing transplant services at NSH-BMT.

Our special thanks to Dr. Gerry Connaghan, who traveled from Dublin, Ireland to attend this special event. Dr. Connaghan was a founding physician of The Blood and Marrow Transplant Group of Georgia.

NSH IRB-BMT Protocols

NSH 922	A Phase II Trial of Total Body Irradiation-Based Myeloablative Conditioning and Transplantation of Partially HLA-Mismatched Peripheral Blood Stem Cells for Patients with Hematologic Malignancies
NSH 928	BMT CTN 0901A Randomized, Multi-Center, Phase III Study Comparing Myeloablative to Reduced Intensity Conditioning Transplants in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia
NSH 959	BMT CTN 0903 – Allogeneic Hematopoietic Cell Transplant for Hematological Cancers and Myelodysplastic Syndromes in HIV-Infected Individuals
NSH 988	BMT CTN 1101 - Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood versus HLA-Haploidentical Related Donor Bone Marrow for Patients with Hematologic Malignancies
	NSH IRB-Leukemia / Lymphoma
NSH 923	A Phase III randomized Study of Oral Sapacitabine in Elderly Patient with newly Diagnosed AML
NSH 952	A Randomized, Multicenter Study Comparing Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-Cell Non-Hodgkin Lymphoma who have relapsed after therapy with CHOP-R or an equivalent regimen and are ineligible for stem cell transplant
NSH 1002	Phase III, Multicenter, randomized Trial of CPX-351 Cytarabine:Daunorubicin Liposome Injection Versus Cytarabine and Daunorubicin in Patients 60-75 years of age with Untreated High Risk (secondary) AML
NSH 1011	An Open-label Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigator's Choice in Adult Patients with Relapsed or Refractory CD22+ ALL
NSH 1021	Assessing the Impact of a simplified Patient Care Strategy to Decrease Early Deaths in Acute Promyelocytic Leukemia (APL) by Maintaining a Database
NSH 1032	A Phase I/Ib Study of Ipilimumab in Patients with Relapsed Hematologic Malignancies After Allogeneic Hematopoietic Cell Transplantation
	Supportive Care NSH-IRB Approved Protocols
NSH 721	NMDP Recipient Consent for Participation in Registry, Research Database, and Research Sample Repository
NSH 888	The Impact of Hematopoietic Stem Cell Transplantation on Primary Caregiver Level of Burden and Distress
NSH 909	A Prospective Assessment of the Diagnostic Utility of Emerging Laboratory Assessments Used in Conjunction with Fiberoptic Bronchoscopy (FOB) in Hematopoietic Stem Cell Transplant (HSCT) and Leukemia Patients with Acute Respiratory Symptoms and Pulmonary Infiltrates
NSH 927	Defibrotide for Patients With Hepatic VOD: A Treatment IND Study
NSH 940	A Unique Schedule of Palonosetron, Ondansetron, and Dexamethasone for the Prevention of Delayed Nausea and Vomiting in Patients Receiving Moderately Emetogenic Myeloablative Chemotherapy
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 1017	Prospective Multi-Center Cohort for the Evaluation of Biomarkers Predicting Risk of Complications and Mortality Following Allogeneic Hematopoietic Cell Transplant (HCT)