6 Fractionated Doses of Gemtuzumab Ozogamicin (GO) Combined to Standard Chemotherapy (CT) Improve Event-Free and Overall Survival in Newly-Diagnosed De Novo AML Patients Aged 50-70 Years Old: A Prospective Randomized Phase 3 Trial From the Acute Leukemia French Association (ALFA)

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Aim. GO is a potent antibody-directed chemotherapy against CD33 antigen. Two MRC and SWOG Phase 3 studies have compared standard CT alone or combined with one single GO infusion (at 3 and 6 mg/m^2,

respectively) in younger adults with AML with contradictory results (Burnett, JCO 2011; Petersdof, Blood 2009). We have shown in relapsed AML Phase 2 studies that fractionated infusion of GO 3 mg/m^2 on day 1, 4 and 7 was effective and might be safely combined to standard 3+7 DNR/AraC induction (Taksin, Leukemia 2007; Farhat, AJH, accepted). Here, we report the results of the prospective open label randomized multicentric Phase 3 ALFA 0701 trial (ClinicalTrial.gov ID, NCT00927498) designed to evaluate the efficacy and safety of adding this fractionated GO schedule to standard front-line chemotherapy in older AML pts.

Methods. Eligible patients (pts) were adults aged 50-70 years old with previously untreated *de novo* AML. Pts were randomized to receive induction with DNR 60 mg/m^2/d on day 1-3 and AraC 200 mg/m^2/d CI on day 1-7, without (DA arm) or with GO at 3 mg/m^2/d on day 1, 4 and 7(DAGO arm). Pts with persistent marrow blasts at day 15 received additional DNR 35 mg/m^2/d on day 1-2 and AraC 1g/m^2/12h on day 1-3. Pts achieving CR/CRp received two consolidation courses with DNR 60 mg/m^2/d on day 1 and AraC 1 g/m^2/12h on day 1-4, ± GO at 3 mg/m^2/d on day 1 according to the randomization arm. The primary study objective was event-free survival (EFS). The study was designed to detect a 25% to 40% EFS gain at 3 years, (two-sided test, power 80%, type I error 5%). Secondary objectives were response rate, disease-free survival (DFS), overall survival (OS), and safety.

Results. From March 2008 to November 2010, the required sample of 280 pts (median age, 62 years) was enrolled. Nine pts did not satisfy for inclusion criteria and were excluded from analysis. Cytogenetics was favorable (N=9), intermediate (N=177), adverse (N= 57), not done/failure (N=28). Overall, 52 pts had a favorable *NPM1*+ w/o *FLT3*-ITD genotype. The two treatment arms were well matched for all pre-treatment characteristics including age, sex, ECOG-PS, WBC, cytogenetics and molecular characteristics. CR+CRp was achieved in 220/271 pts (77%): 100/134 (75%) in the control DA arm *versus* 110/137 (80%) in the DAGO arm (P=0.31). There were 5/134 (4%) induction deaths in DA arm and 9/137 (6%) in DAGO arm (P=0.41). Primary resistant AML rate was 29/134 (22%) after DA *versus* 18/137 (13%) after DAGO (P=0.08). At 2 years, EFS was estimated at 15.6% in DA arm *versus* 41.4% in the DAGO arm (P=0.0018), while DFS was 18.1% in DA arm and 48.5% in the DAGO arm (P=0.0009). This significant benefit in EFS (primary objective) was observed in pts aged <65 years (P=0.035) as well as in older pts (P=0.019), and persisted after censoring the 39 pts who received allogeneic stem cell transplantation in first CR/CRp at transplant time (P=0.015). Subgroup analysis showed that EFS benefit persisted in pts with favorable/intermediate karyotype (P=0.0008) while not in those with adverse karyotype (P=0.25). Interestingly, EFS benefit was still observed when excluding favorable pts (favorable karyotype or genotype) from the comparison (P=0.0017). Finally, in the whole patient population, this gain in EFS translated into a longer OS (median, 25.4 *versus* 15.3 months in DAGO *versus* DA pts; P=0.037). Besides treatment arm, cytogenetics and favorable genotype were the only factors predictive of outcome. After adjustment on these factors, DAGO treatment remained significantly associated with longer EFS (P=0.009), DFS (P=0.003), but not OS (P=0.14). The rate of fatal adverse events at least possibly attributable to treatment was 9/134 (6.7%) in the DA and 12/137 (8.7%) in the DAGO arm (P=0.65). Prolonged grade ≥ 3 thrombocytopenia was observed in 19 DAGO pts, either after induction (N= 4) or first consolidation (N=15). Three liver VOD were observed in the DAGO arm (2 during induction, 1 during first consolidation), 2 being associated with a fatal issue. No difference was observed

between both arms in the incidence of severe sepsis (DAGO 18.9%, DA 14%), as well as in the rate of intensive care unit admission during the course of therapy (DAGO 14.5%, DA 12.6%).

Conclusion. The addition of fractionated doses of GO (3 mg/m^2/d on day 1, 4, and 7) to standard CT significantly improves EFS and to a less degree OS in AML pts aged 50-70 years old. The main toxicity observed with GO was prolonged thrombocytopenia in 19 patients and 3 episodes of VOD.

167 B-Cell Depletion, Remissions of Malignancy, and Cytokine-Associated Toxicity in a Clinical Trial of T Cells Genetically-Engineered to Express An Anti-CD19 Chimeric Antigen Receptor

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New therapies are needed for chemotherapy-resistant B-cell malignancies. Adoptive transfer of T cells genetically-engineered to express chimeric antigen receptors (CARs) that specifically recognize the B-cell antigen CD19 is a promising new approach for treating B-cell malignancies. We are conducting a clinical trial in which patients receive infusions of autologous T cells that are transduced with gamma-retroviruses encoding an anti-CD19 CAR. The CAR is made up of the variable regions of an anti-CD19 antibody, a portion of the CD28 molecule, and a portion of the CD3-zeta molecule. Our clinical protocol consists of cyclophosphamide plus fludarabine chemotherapy followed by an infusion of anti-CD19-CAR-transduced T cells and a course of high-dose IL-2. We have treated 8 patients on this clinical trial. Four of the patients had chronic lymphocytic leukemia (CLL), and 4 patients had B-cell lymphoma. Anti-CD19-CAR-transduced T cells that specifically recognized CD19-expressing target cells were produced for all patients. The total number of cells administered to each patient ranged from $0.5x10^7$ to $5.5x10^7$ cells per kg of bodyweight. A mean of 54% of the administered cells expressed the anti-CD19 CAR. One patient with CLL obtained a complete remission that is ongoing 15 months after treatment. Five patients obtained partial remissions that are ongoing in 3 patients. One patient with CLL had stable disease. One patient with lymphoma died of culture-proven influenza A pneumonia and is not evaluable for lymphoma response. A striking depletion of $CD19^+$ B-lineage cells occurred in 4 of 8 patients. This B-cell depletion lasted for up to 15 months, and it is ongoing in 3 of 4 patients. Because of the long duration of B-cell depletion, it cannot be attributed to the chemotherapy that the patients received. For example, a patient with follicular lymphoma had a normal level of polyclonal blood B cells before treatment on our protocol. Six months after treatment, he had a blood B cell count of 1/microliter (normal range 61-321 B cells/microliter). A patient with CLL had a regression of adenopathy in the first

32 days after chemotherapy and CAR-transduced T cell administration. Interestingly, this adenopathy continued to substantially regress between 33 and 133 days after chemotherapy ended. CAR-transduced cells were detected in the blood of all 8 patients by quantitative PCR. The percentage of peripheral blood mononuclear cells (PBMC) containing the CAR gene varied widely, but in 2 patients the CAR gene was detected in greater than 0.1% of PBMC more than 90 days after infusion. At early time-points after infusion, CAR-expressing T cells constituted up to 20% of all blood T cells. Patients had significant toxicity during the first 10 days after CAR-transduced T cell infusion. The most prominent toxicity was hypotension. Sharp increases in serum interferon gamma (IFN) and tumor necrosis factor (TNF) occurred in 4 of 8 patients during the first 10 days after cell infusion. In the 4 patients with prominent elevations in inflammatory cytokines, peak serum IFN levels ranged from 865 to 2305 pg/mL, and peak TNF levels ranged from 49 to 118 pg/mL. As measured by an objective sequencial organ failure assessment score, the 4 patients with prominent elevations in IFN and TNF had more severe clinical toxicity during the first 10 days after cell infusion than the other 4 patients who did not have prominent elevations of IFN and TNF. We analyzed PBMC of three patients with elevations of serum IFN and TNF by using an ex vivo assay consisting of a 6-hour incubation of PBMC with target cells followed by intracellular cytokine staining. In all three patients, we detected T cells that produced IFN and TNF in a CD19-specific manner in PBMC samples collected after anti-CD19-CAR-transduced T cell infusions but not in PBMC samples collected before CAR-transduced T cell infusions. This indicates that anti-CD19-CAR-transduced T cells were a source of the elevated serum cytokines. In multiple patients receiving infusions of anti-CD19-CAR-transduced T cells, we have demonstrated elimination of $CD19^+$ B-lineage cells, regressions of malignancy, elevated levels of serum inflammatory cytokines, and CD19-specific T cells that produce inflammatory cytokines ex vivo. These results demonstrate that CAR-expressing T cells can specifically eliminate targeted cells and cause significant cytokine-mediated toxicity in humans.

817 Over-Expression of TRAIL on Donor T Cells Enhances GVT and Suppresses Gvhd Via Elimination of Alloreactive T Cells and Host APC

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Strategies to suppress GVHD are often associated with broader suppression of the immune system leading to a compromised GVT effect. Using experimental models, we have demonstrated a novel strategy to enhance GVT effects and explicitly suppress GVHD using genetically engineered T lineage cells over-expressing TNF-Related Apoptosis Inducing Ligand (TRAIL). TRAIL can induce apoptotic

signals through death receptor (DR) 4 and 5 molecules (only DR5 in mice) expressed on target cells. Expression of DR5 is higher on certain tumors and can be enhanced on others using small molecules rendering them susceptible to TRAIL mediated killing. TRAIL is therefore an attractive candidate for genetic engineering of donor T cells to enhance their GVT potential. We evaluated the effect of TRAIL over-expression (TRAIL+) in donor T cells (mature and precursor) on GVHD and GVT. Mature T cells derived from donor B6 splenocytes were transduced with a lentiviral TRAIL expression vector. The transduced TRAIL+ T cells were adoptively transferred on day 0 into lethally irradiated CBF1 recipients of T cell depleted allografts and LB27.4 tumor (B6 ?/span> CBF1+LB27.4) to assess their GVHD and GVT activity. TRAIL+ T cells displayed significantly enhanced antitumor immunity compared to T cells transduced with a control vector against LB27.4 tumor cell lines in vitro and upon transfer into tumor bearing allo-BMT recipients ($p<0.01$, 100% survival in TRAIL+ T cell group) (Fig 1A, also shown at the annual meeting last year). Precursor (pre)T cells have the benefit of regenerating the T cell compartment without causing GVHD and being available for "off the shelf" use. We generated TRAIL+ preT cells from transduced B6 hematopoietic stem cells and expanded them using the OP9-DL1 co-culture system. Adoptive transfer of B6 TRAIL+ preT cells into syngeneic-transplanted BALB/c mice could reconstitute the T cell compartment with TRAIL-expressing T cells and caused enhanced antitumor activity ($p<0.05$) compared to mock (GFP)-transduced controls.

Interestingly, in addition to enhanced GVT, the recipients treated with TRAIL+ T cells had significantly less GVHD lethality and morbidity (Fig1B). This was observed across multiple GVHD models (B6 ?/span> CBF1, B6?/span> BALB/c and B10.BR?/span> B6). To explore the factors contributing to TRAIL-mediated suppression of GVHD, we used animals deficient in DR5 (DR5ko) in our models of GVHD. We found that GVHD suppressive effects of TRAIL were lost when hosts were DR5ko or when DR5ko TRAIL+ T cells were adoptively transferred indicating that TRAIL+ T cells suppress GVHD by targeting both host and donor compartments. We observed a higher DR5 expression in host MHC-II^{hi} antigen presenting cells (APC) following total body irradiation, suggesting that TRAIL+ donor T cells could potently eliminate host APC, resulting in less GVHD. Further, on transferring wild type T cells into irradiated hosts, we found that alloreactive CD25+ T cells had a significantly higher DR5 expression compared to CD25- T cells. This indicates that TRAIL+ T cells can specifically target the alloreactive CD25+ T cells in order to suppress GVHD.

Collectively, our data demonstrate that donor T cells genetically engineered to express TRAIL can enhance GVT effects and suppress the development of lethal GVHD in recipients of allo-HSCT. Our data suggests that his suppression of GVHD is mediated by the elimination the alloreactive donor T cells and the elimination of GVHD-promoting residual APC. Furthermore, we demonstrated that allogeneic ex vivo generated preT cells expressing TRAIL could mediate a strong protection against tumor challenge in syngeneic HSCT recipients. TRAIL over-expression thus represents a potential off the shelf approach to enhancing GVT in both allogeneic and autologous transplantation. Despite elimination of alloreactive donor T cells, TRAIL+ T cells demonstrated enhanced GVT by directly targeting DR5+ tumors in the absence of alloreactivity.

1 Increased Incidence of Chronic Graft-Versus-Host Disease (GVHD) and No Survival Advantage with Filgrastim-Mobilized Peripheral Blood Stem Cells (PBSC) Compared to Bone Marrow (BM) Transplants From Unrelated Donors: Results of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Protocol 0201, a Phase III, Prospective, Randomized Trial

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Background: Randomized trials demonstrated that filgrastim-mobilized PBSC compared to BM from HLA-identical siblings improved engraftment kinetics, increased risks of acute and chronic GVHD, but also decreased relapse and improved survival in patients with high risk leukemia. Retrospective analyses of unrelated donor transplants did not appreciate the same PBSC protective effect.

Patients and Methods: The BMT CTN, sponsored by the NHLBI and NCI, conducted a Phase III, randomized, multicenter, trial of unrelated donor PBSC versus BM. The primary objective was to compare two-year survival probabilities in the two study arms using an intent-to-treat analysis. Both patients and donors provided informed consent. Fifty centers in the U.S. and Canada enrolled patients between

January, 2004 and September 2009. Median follow up is 36 months (interquartile range 25 ?37 months). Randomization was performed in a 1:1 ratio to either PBSC or BM and stratified by transplant center and disease risk. Of the 278 subjects randomized to BM, 5% had no transplant, and 4.3% crossed over to PBSC; of the 273 randomized to PBSC, 4% had no transplant, and 0.4% crossed over to BM, so subjects on both arms had greater than 90% compliance with the assigned therapy. Patient primary disease (AML, ALL, CML, MDS, CMML, and MF), disease risk, gender, age, race, ethnicity, CMV serology, performance status, comorbidity, organ function, conditioning regimen, GVHD prophylaxis, use of growth factors, and donor characteristics were all well balanced between the two groups. Overall, 90% were adults over age 20, 47% had AML, 28% had high risk disease, 48% were conditioned with cyclophosphamide plus total body irradiation, and 71% received tacrolimus plus methotrexate for GVHD prophylaxis.

Results: There were no observed differences in outcomes between the two groups except for a higher incidence of overall chronic GVHD (see Table) and more common chronic extensive GVHD with PBSC (46% vs. 31%). There were no survival differences according to graft sources in planned subset analyses of low and high risk malignancy or in those received HLA-matched or mismatched grafts. Primary causes of death were relapse in 54% vs. 49%, graft failure in 7% vs. 0%, acute or chronic GVHD in 22% vs. 34%, others in 16% vs. 16% of the BM and PBSC arms, respectively.

Conclusion: This large randomized trial shows that PBSC from unrelated donors is associated with higher rates of chronic GVHD compared to BM, although rates of acute GVHD, relapse, non-relapse mortality and overall survival are similar.

841 Burden of Morbidity in 10+ Year Survivors of Hematopoietic Cell Transplantation (HCT): A Report From the Bone Marrow Transplant Survivor Study (BMTSS)

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Background: High-intensity therapeutic exposures and prolonged immunosuppression increase the risk of long-term complications after HCT, with an attendant increase in the healthcare needs of these long-term survivors. We have previously demonstrated that morbidity increases with increasing time after HCT (Sun CL, Blood, 2010;116:3129-39). However, the burden of morbidity in patients who survive extended lengths of time after HCT and the consequent healthcare needs of these survivors are unknown.

Methods: Utilizing resources offered by the BMTSS, we evaluated the risk of chronic health conditions and psychological health of 366 10+ year HCT survivors and their siblings (n=309). A severity score (grade 1 [mild]; grade 2 [moderate], grade 3[severe], grade 4 [life-threatening], and grade 5 [death

due to chronic health condition]) was assigned to each health condition using the CTCAE, v3.0. Cumulative incidence of chronic health conditions was evaluated, using competing risks method. Brief Symptom Inventory (BSI) was used to describe adverse psychological health. Multivariate regression analysis allowed identification of vulnerable subgroups. The current status of healthcare utilization by the HCT survivors was also evaluated.

Results: The mean age at HCT was 22 years (range: 0.4-59.8) and at study participation was 37 years (range: 11-72); mean length of follow-up was 15 years (range: 10-28). Primary diagnoses included AML (28%), ALL (17%), CML (17%), NHL (11%), aplastic anemia (11%), HL (7%), and other diagnoses (9%). Stem cell graft was autologous (27%); allogeneic related (65%) and unrelated donor (8%); 72% of the patients received TBI-based conditioning. At least one chronic health condition was reported by 74% of the HCT survivors, compared with 29% of siblings ($p<0.001$); 25% of the survivors reported severe/life-threatening conditions compared to only 8% of the siblings ($p<0.001$). Commonly reported severe/life-threatening chronic health conditions included myocardial infarction, stroke, blindness, diabetes, musculoskeletal problems, and subsequent malignancies. As shown in Figure 1A, the 15-year cumulative incidence of any chronic health condition (grades 1-5) was 71% (95% CI, 67-75%), and of severe-life-threatening conditions or death was 40% (95% CI, 33-47%). HCT survivors were 5.6 times as likely to develop a severe/life-threatening condition (95% CI, 3.7-8.6), compared with age- and sex-matched siblings. The cumulative incidence of severe/ life-threatening conditions did not differ by type of HCT ($p=0.79$, Figure 1B). Using BSI, we evaluated somatic distress, anxiety, and depression among HCT survivors and their siblings. While the prevalence of anxiety and depression were comparable between survivors and siblings, HCT survivors were 2.7 times more likely to report somatic distress ($p<0.001$). Among survivors, female gender (OR=3.6, 95% CI, 1.4-9.0), low household income (<$20,000 OR=4.4, 95% CI, 1.1-17.2), and poor self-rated health status (OR=10.6, 95% CI, 4.0-27.9) were associated with increased risk for somatic distress. Fortunately, 90% of HCT survivors carried health insurance coverage, because a high proportion needed ongoing specialized medical care; 69% of the HCT survivors reported cancer/HCT-related visits at an average of 15 years after HCT.

Conclusions: The burden of long-term physical and emotional morbidity borne by 10+ year HCT survivors is substantial, resulting in a high utilization of specialized healthcare. Patients, families and healthcare providers need to be made aware of the high burden, such that they can plan for post-HCT care, even many years after HCT.

590 Final Analysis of a Randomized Comparison of ABVD Chemotherapy with a Strategy That Includes Radiation Therapy (RT) in Patients with Limited-Stage Hodgkin Lymphoma (HL): NCIC CTG/ECOG HD.6

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Background: The NCIC CTG / ECOG HD.6 trial is based on the hypothesis that for patients with limited-stage HL, treatment with single-modality ABVD provides comparable disease control, is associated with a reduced incidence of deaths due to late treatment effects and thus might improve long-term survival in comparison with treatment that includes extended-field RT. In this randomized controlled phase III trial, our primary objective was to compare the 12-yr overall survivals (OS) of limited-stage HL patients treated with ABVD alone with those receiving therapy that includes RT. Secondary outcomes include freedom from disease progression (FFDP), in which those dying prior to disease progression are censored, and event-free survival (EFS), in which the first of disease progression or death is considered an event. 營 n 2005, we published 5-yr outcomes (median follow-up 4.2 yrs [Meyer, J Clin Oncol]). We now report results of the final analysis.

Methods: Eligible patients had non-bulky clinical stage I-IIA HL; patients with subdiaphragmatic disease were eligible if disease was confined to the iliac, inguinal and/or femoral regions. Prior to randomization, patients were stratified into low and high-risk categories; low-risk patients had all of lymphocyte predominant or nodular sclerosis histology, age < 40 yrs, ESR < 50, and involvement of 3 or fewer disease-site regions; all others were high-risk. Patients randomized to therapy that includes RT received single-modality subtotal nodal irradiation (STNI) if low-risk and combined-modality ABVD (2 cycles) plus STNI if high-risk. All patients randomized to the experimental arm received single-modality ABVD (4 cycles); those not demonstrating a complete remission with restaging after 2 cycles received 6 cycles. Between March 1994 and April 2002, 405 patients were entered; 399 were eligible and included in the primary analysis (modified intent o-treat [ITT]). The clinical cut-off date for follow-up was 2010/DEC/31 and the database was locked on 2011/JUL/15. All P-values are 2-sided.

Results: The median duration of follow-up is 11.3 yrs. The OS was superior in patients randomized to ABVD (P=.04; HR=0.5; 12-yr estimates 94% vs. 87%). In comparison with patients randomized to therapy that includes RT, FFDP trended to being inferior in patients randomized to ABVD (P=.07; HR=1.82; 12-yr estimates 88% vs. 92%); no differences in EFS were detected (P=.5; HR=0.87; 12-yr estimates 86% vs. 80%). Sensitivity analyses included a true ITT evaluating all randomized patients and adding data obtained between the clinical cut-off and data-lock dates; results were robust and yielded

similar findings.?Causes of death in ABVD vs. RT-arm patients (N = 12 vs. 24) included HL or early treatment complication (6 vs. 4), second cancers (4 vs. 9), and other (2 vs. 11). 燗nalysis of high-risk patients allocated to ABVD (N=137) vs. ABVD+STNI (N=139) showed similar respective results to the primary analysis: in comparison with those randomized to RT, OS was superior in the ABVD arm (12-yr estimates 92% vs. 81%; HR=.47; P=.04), FFDP was inferior (12-yr estimates 87% vs. 94%; HR=3.03; P=.01) and no differences in EFS were detected (12-yr estimates 84% vs. 78%; HR=.87; P=.6). Late-effects trended to being less frequent in ABVD patients, including second cancers (6.1% vs. 10.8%) and cardiac events (9.7% vs. 14.8%).

Conclusions: We conclude that in patients with limited-stage HL, ABVD improves OS as compared with treatment that includes STNI, including combined modality therapy, because it is associated with fewer deaths from causes other than HL. The HD.6 trial hypothesis was thus confirmed. With respect to modern RT approaches, the implications of our results are: i) at 12 years, 88% of patients are disease-free and more than 90% are alive when initially treated with ABVD alone; ii) limitations exist in using FFDP as a proxy measure for OS when late treatment effects may occur; and, iii) when treatment strategies have competing risks, long-term follow-up provides crucial insights into the interpretations of best therapy.