June 14, 2016

FACT Clinical Outcomes Improvement Committee

RE:

Dear Committee Members,

This letter addresses the requests in your email dated May 18, 2016. Thank you for the opportunity to update the committee regarding the one year survival in our ***adult allogeneic transplant population from 2011 to the present.*** We will also inform you of quality improvement initiatives undertaken. Our response is divided into three sections and will address the requests of the committee.

Briefly, a number of active changes were made in late 2013 (early 2014) to improve the survival of our allogeneic transplant recipients. Some of these changes include the following issues noted below, with details listed in the subsequent sections:

- We have restructured the allogeneic patient selection process.
- Each preparative and immunosuppression regimen was reviewed, revised and changed, using evidence-based practices.
- Our QA/QI program, always a very strong aspect of our program, has expanded to address additional aspects of allogeneic recipients, including caregiver support post-transplant, psychosocial issues etc.

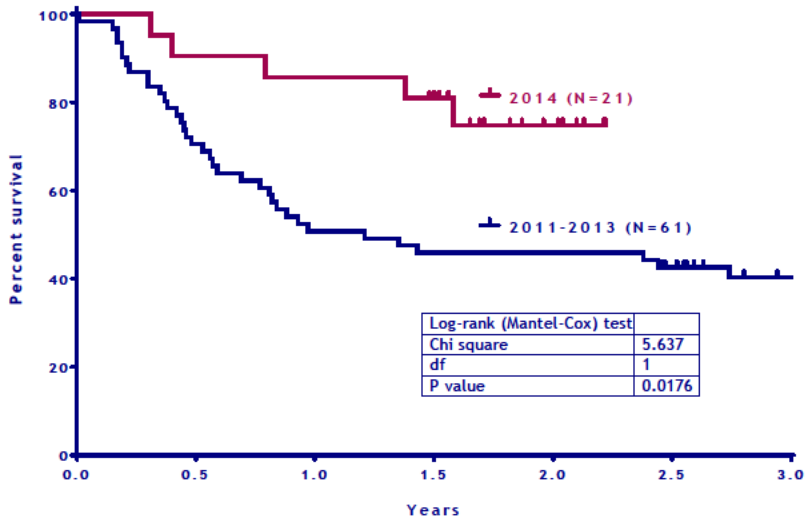
Section 1.0 Background information: Improvement in Survival since 2011

Table 1 demonstrates the improvement in allogeneic recipients' survival, dating back to 2011. The impressive improvements in day 100 and one year mortality rates are due to the adjustment and changes noted above. **Figure 1** depicts Kaplan-Meier survival curves, for the years listed.

Table 1: Survival Rates for first allogeneic transplant recipients

	2011-2013 (n=65)	2012-2014 (n=64)	2014 (n=23)
Day 100	86.9%	93.4%	100%
1 Year	50.8%	67.2%	85.7%

Figure 1: Kaplan-Meier survival estimates for allogeneic transplant recipients



Section 2.0 Quality Improvement Changes Implemented to Improve Survival in Allogeneic Recipients

- We have restructured the allogeneic patient selection process.
- Each preparative and immunosuppression regimen was reviewed, revised and changed, using evidence-based practices.
- Our QA/QI program, always a very strong aspect of our program, has expanded to address additional aspects of allogeneic recipients, including caregiver support post-transplant, psychosocial issues etc.

1. Restructuring of the allogeneic patient selection process

Our current patient selection process is quite rigorous. We evaluate each patient in detail using the following processes:

- Each potential allogeneic patient is presented twice (minimum) to the group of transplant clinicians to identify the treatment for optimal survival and a durable remission. The first presentation is to our BMT Tumor Board. The second presentation involves a more in-depth patient review focusing on treatment options, co-morbidity score, psychosocial issues, discussion of the preparative regimen, type of allogeneic transplant, and summary of the literature.

- This strict process of patient selection follows NMDP guidelines and eligibility criteria. Additional criteria include:
  - Patients with high co-morbidity scores (Hematopoietic Cell Transplant - Comorbidity Index) are ineligible for transplant.
  - Patients with acute leukemia not in complete remission are ineligible.
  - Patients with a hematologic malignancy that is chemo-resistant are ineligible.
  - Patients in partial remission are discussed in detail to determine if transplant offers the best treatment option.

2. **Revised Preparative and Immunosuppression Regimens**

As noted above, in late 2013, the BMT Program reviewed, altered or changed each allogeneic treatment regimen and each immune suppressive regimen. These changes resulted in an immediate impact. For example, the one year survival for allogeneic recipients in 2013 was 57%. In 2014, with the change to a fludarabine/busulfan-based treatment regimen, as well as changes in the immunosuppressive regimens, the one year survival rate for allogeneic recipients jumped to 85.7%!!! To date, we have transplanted 25 allogeneic recipients using the Flu/Bu/ATG regimen, with impressive survival rates (Refer to **Table 2** below).

Table 2: Fludarabine/Busulfan/ATG Myeloablative Allogeneic Transplants

Table 2a: Flu/Bu/ATG Patient Information

Diagnosis	*# of Patients*	*Matched Related Donor*	*Matched Unrelated Donor*
AML	14	6	8
MDS	6	3	3
MPN	5	3	2
Total	*25*	*12*	*13*

Table 2b: Flu/Bu/ATG Survival

Follow-up	
Median	10 months (range: 1-30 months)
Alive	n=21 of 25 patients
Deceased	n=4 patients at median of 10 months (range 3-19)
AML	n=2 (3 and 7 months)
MPN	n=2 (17 and 19 months)

We continue to observe this marked improvement in survival rates, at both day 100 and at one year and beyond. The lower rates noted prior to 2013 no longer occur. Please keep this in mind when reviewing the survival results.

3. **Changes to our QI/QA Initiatives Focused on Allogeneic Transplant Patients**

- We continually review and update our clinical pathways and SOPs, using evidence-based practices. For example, please find our current pathway (attached) addressing treatment of AML patients who relapse following allogeneic transplant. (**Figure 2**) This paradigm was developed after a review of recent literature on the subject. **Table 3** is a summary of the pertinent references and facts.
- Our Program takes pride in the quality of our QI/QA program. Our Program continues to examine ways to improve outcomes and efficiency, while decreasing complications. Some of the ongoing efforts, including our publications, are listed below.
  - In an effort to minimize any re-admissions post-transplant, we worked with the and examined our re-admission rates following transplantation.

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- To improve efficacy and minimize costs, we evaluated ways to improve platelet transfusions in transplant recipients.
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- We defined a clinical pathway and identified resource utilization for allogeneic transplant patients who are receiving ECP for treatment of GVHD.
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- We have examined our use of ECP for the treatment of GVHD.
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- We identified that blood sampling was similar to marrow sampling to quantify donor chimerism following allogeneic transplantation. This has decreased the number of post-transplant marrow biopsies that we perform.
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Section 3.0 Causes Of High Mortality Rates

The Committee asked that we review and address the cause of mortality for each patient from 2011 to 2013. The causes of our one year mortality between 2011 and 2013 was due to transplanting high risk patients based on:

- Disease responsiveness – Almost 40% of the transplanted patients demonstrated refractory disease or only a partial remission at the time of transplant (25 of 65 patients). This resulted in the following eligibility criteria for each potential allogeneic patient:
  - Patients with acute leukemia not in complete remission are ineligible.
  - Patients with a hematologic malignancy that is chemo-resistant are ineligible.
  - Patients in partial remission are discussed in detail to determine if transplant offers the best treatment option.

- High comorbidity scores – Approximately 30% of transplanted patients entered transplant with a HCT-CI ≥ 3 (18 of 65 patients). As a result, we have implemented the following eligibility criteria for each potential allogeneic patient:
    - Patients with high co-morbidity scores (Hematopoietic Cell Transplant - Comorbidity Index) are ineligible for transplant.

- Older age – Twenty percent of the transplanted patients were over 65 years of age (13 of 65 patients). As a result, any potential allogeneic patient age 60 or over is thoroughly evaluated prior to acceptance.

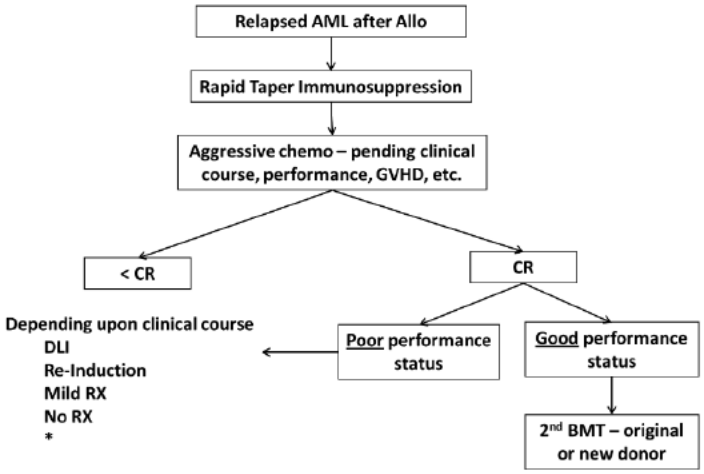
As per the Committee's request, we have enclosed the specific cause of death for each patient. Please see **Table 4** for the specific causes of death and patient demographics.

I am hopeful that our comments will explain the rationale for the previously noted inferior outcomes. With the changes implemented above, the survival rates for allogeneic recipients has markedly improved and continue to today. We look forward to your review of our data. I would be happy to review these results with you.

Sincerely,

ENCLOSURES:

Figure 2: Treatment pathway for AML relapsed after allogeneic transplant.



* If remission after BMT #1 > 6 months, w/ good performance → consider BMT

Table 3: Summary of recent literature on treatment of relapsed AML following allogeneic transplant.

Study	*# Pts*	*Treatment*	*Survival*	*Comments*
USA (all pts) *JCO 2002, 20:405*	*65*	*7+3 all pts; then DLI*	*At 2yrs: 19%* *If in CR = 41%* *< CR = 5%*	*Improved survival if:* *1) Remission duration > 6 months after #1* *2) CR after re-induction*
EBMTR (RIC/NMA) *Blood 2012, 119:1599*	*263*	*Varied (see slide)*	*At 2yrs* *OS = 14%*	*Improved survival if:* *1) Remission duration ≥ 5 months.* *2) ≤ 25% blasts at relapse*
German Registry (all pts) *JCO 2013, 31:3259*	*179*	*99% pts received chemo → BMT*	*At 2 yrs.* *OS = 25%*	*Improved survival if:* *1) Remission ≥ 6 months.* *2) CR after re-induction* *3) **worse survival if #1 is MUD*
Australian Registry (all pts) *BBMT 2014, abstr. 25*	*386*	*Varied*	*OS at 5 years* *Chemo 5%* *DLI/BMT 23%*	*Improved survival if:* *1) Remission ≥ 6 months* *2) No GVHD w/ RX* *3) Pts receive DLI or HSCT*
U Chicago (RIC/NMA) *BMT 2007, 40:1027*	*25*	*Varied*	*At 2yrs* *OS = 20%*	*Improved survival if:* *1) Pts receive HSCT or DLI* *2) Longer remission* *3) ? Donor chimeras at relapse* *4) Decrease % marrow blasts* *5) No new cytogenetic abn*
Korean *Leukemia 2004, 18:1789*	*16*	*Cytarabine/Ida Etoposide (G-primed w/ CD34+ cells*	*2yr OS = 31%* *If remission > 6 months = 51%* *If remission < 6 months = 0%*	*Improved survival:* *1) If remission > 6 months.*

Table 3: References

1. Christopeit M, Kuss O, Finke J, et al. Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. J Clin Oncol. 2013;31(26):3259-71. doi:10.1200/JCO.2012.44.7961
2. Schmid C, Labopin M, Nagler A, et al. Treatment, risk factors, and outcome of adults with relapsed AML after reduced intensity conditioning for allogeneic stem cell transplantation. Blood. 2012;119(6):1599-606. doi:10.1182/blood-2011-08-375840
3. Pollyea DA, Artz AS, Stock W, et al. Outcomes of patients with AML and MDS who relapse or progress after reduced intensity allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2007;40(11):1027-32.
4. Choi SJ, Lee JH, Lee JH, et al. Treatment of relapsed acute myeloid leukemia after allogeneic bone marrow transplantation with chemotherapy followed by G-CSF-primed donor leukocyte infusion: a high incidence of isolated extramedullary relapse. Leukemia. 2004;18(11):1789-97.
5. Levine JE, Braun T, Penza SL, et al. Prospective trial of chemotherapy and donor leukocyte infusions for relapse of advanced myeloid malignancies after allogeneic stem-cell transplantation. J Clin Oncol. 2002;20(2):405-12.
6. Lim ABM, Curley C, et al. The Australian Experience with Relapsed Acute Myeloid Leukemia Post Allogeneic Hematopoietic Stem Cell Transplantation Yields a Simple Prognostic Index for Survival after Relapse. Biology of Blood and Marrow Transplantation Vol. 20, Issue 2, Supplement, Pages S38-S39.

Table 4: Patient Demographics and Cause of Death 2011 – 2013.

#	Sex	Age	Dx	Dx Subtype	Date TR	# TR	First Allo?	Allo Type	Donor	Preparative Regimen	Disease Status	Death Days	Cause of Death