Autologous/reduced-intensity allogeneic stem cell transplantation versus autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study

Running title: Allogeneic transplantation in multiple myeloma

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Key points:

- Tandem autologous/reduced intensity allogeneic transplantation is superior to autologous transplantation alone in multiple myeloma

Abstract

Long-term follow up of prospective studies comparing allogeneic transplantation to autologous transplantation in multiple myeloma are few and controversial. This is an update at a median follow up of 96 months of the EBMT NMAM2000 myeloma study that prospectively compares tandem autologous/reduced intensity conditioning allogeneic transplantation (auto/RICallo) to autologous transplantation alone (auto). 357 myeloma patients up to the age of 69 years were enrolled. Patients with an HLA-identical sibling were allocated to auto/RICallo (n=108) and those without to auto alone (n=249). At 96 months progression-free survival (PFS) and overall survival (OS) were 22% and 49% versus 12% (p=0.027) and 36% (p=0.030) with auto/RICallo and auto respectively. The corresponding relapse/progression rate (RL) was 60% versus 82% (p=0.0002). Non-relapse mortality at 36 months was 13% versus 3% (p=0.0004). In patients with the del(13) abnormality corresponding PFS and OS were 21% and 47% versus 5% (p=0.026), and 31% (p= 0.154). Long-term outcome in patients with multiple myeloma was better with auto/RICallo as compared to auto only and the auto/RICallo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Follow up longer than 5 years is necessary for correct interpretation of the value of auto/RICallo in multiple myeloma.
Introduction

Despite improvements in survival of multiple myeloma patients by treatment with new drugs like thalidomide, bortezomib and lenalidomide, documented cures of the disease are lacking. Allogeneic hematopoietic stem cell transplantation has been studied, but results have been controversial. Recently, we published the first results of a prospective study (NMAM2000) comparing tandem autologous (auto)/reduced intensity conditioning allogeneic transplantation (RICallo) with autologous transplantation – single (auto) or tandem(auto/auto). Although a superior progression-free survival (PFS), overall survival (OS) and relapse rate (RL) using the tandem auto/RICallo treatment modality was documented using appropriate tests for crossing curves, the interpretation of the results has been controversial. The present update of the study, after a median follow-up time of 96 months, supports and strengthens the previous conclusion that the tandem auto/RICallo approach prolongs PFS and OS long term due to lower progression/relapse rate. This is true both using an intention to treat analysis and an analysis comparing only those patients who received treatment according to protocol. Considering this study started in the era predating “novel” agents, our results suggest that reports of the “death” of allogeneic transplantation are greatly exaggerated.

Patients and Methods

Patients

The study design was presented previously. Briefly, patients were included in this study from February 2001 to January 2005. Three-hundred and fifty-seven patients up to the age of 69 who had a response better than progression to first-line induction treatment were enrolled. All patients had undergone HLA typing and 108 of them had a HLA-identical sibling and were assigned to the auto/RICallo treatment arm. Two-hundred and forty-nine patients without a matched sibling were allocated to the auto arm. Single or tandem auto was optional in the auto arm. Two patients in the auto/RICallo arm did not have a HLA-identical donor but did have a sibling donor with one HLA mismatch. They were mistakenly treated according to the auto/allo arm protocol and were included in this arm in the intention to treat analysis. Patient characteristics at inclusion were evenly distributed with the exception of age at diagnosis,
which was slightly higher in the auto group (median 57 years versus 54 years in the auto/RICallo group) as previously presented. Median time of follow-up after inclusion at the first auto was 96 months (range 47-127 months) as compared to 61 months in our previous report. The study was approved by the Ethical committee (Internal Review Board) of the Karolinska Institute and conducted in accordance with the Declaration of Helsinki.

Analysis of chromosomal aberrations

Cytogenetic analysis of the chromosome 13 deletion (del(13q14)) was performed in 214 patients using fluorescent in situ hybridization (FISH) as previously described. The del(13) aberration was present in 92 patients, 29 of whom were in the auto/RICallo group and 63 in the auto group. One-hundred and twenty-two patients were negative for del(13), 34 in the auto/allo group and 88 in the auto group, respectively. Although del(13) is not an optimal prognostic marker for outcome after auto, at the time this was the only chromosomal aberration that could be adequately analyzed in most centers. It is still of some value since it is often associated with new better prognostic chromosomal makers indicating poor prognosis after auto (del(17p), t(14;16), t(14;20))

Treatment regimens and response criteria

Prior to inclusion in the study, patients received induction chemotherapy with the VAD regimen (vincristine, doxorubicin and dexamethasone) or with regimens similar to VAD. Seventy-three percent of the patients in the auto/RICallo arm and 67 % in the auto arm received the VAD regimen, while a mixture of regimens were used in other patients. Novel drugs like thalidomide, lenalidomide and bortezomib were not used prior to relapse/progression. All patients with at least stable disease after the induction therapy were included in the study and received an autologous transplant.

Out of the 108 patients allocated to the auto/RICallo arm, 92 received the tandem auto/RICallo transplantation according to protocol (one more patient as compared to the previous report was found to have been treated according to protocol). The 16 patients that did not receive their planned RICallo were described previously. The RIC regiment consisted of fludarabine 30 mg/m²/day for three days + total body irradiation (TBI) 2 Gy. Prevention of
graft-versus-host disease (GVHD) was performed with cyclosporin and mycophenolate mofetil as previously described.

Patients without a matched sibling donor received either no further treatment (n = 145) or at the discretion of the center a second auto as part of a tandem transplantation program. The conditioning for the second autograft was the same as for the first (melphalan 200 mg/m²).

After progression treatment was optional. In the auto/RI Callo group 18 patients received donor lymphocyte infusions (DLI), 2 erroneously before progression, 4 within 2 months from progression and 12 later. Nine patients received another allograft and 5 an autograft. Other patients received a variety of treatments including chemotherapy and new drugs. In the auto group 44 patients received an additional autograft, 10 within 2 months from progression and 34 later. Two patients received RICallo within 2 months from progression and 11 patients received an allograft later, 2 of them as a tandem auto/RI Callo. All other patients received a variety of chemotherapy regimens, radiotherapy and new drugs like thalidomide, bortezomib and lenalidomide. Since the use of novel drugs was optional after progression meaningful analysis of their impact could not be performed.

The EBMT response criteria were used as previously described¹¹.

Statistical methods

The primary end point was PFS from the time of inclusion in the study (i.e. from the date of the first auto). Secondary end points were OS, RL, complete remission rate (CR) and non-relapse mortality incidence (NRM). Detailed definitions and statistical methods used have been described previously⁸. Due to crossing survival curves the standard Log-Rank test was not valid, and appropriate tests for differences in the long-term outcomes were used, specifically the method based on the “cloglog” transform of survival functions, as suggested by Klein et al¹². The comparison of OS and PFS was reported at 60 and 96 months (respectively a standard timing and the median follow-up). The median follow-up of OS after progression was 66 months, therefore only the difference at 60 months from progression was reported. Additionally to these tests, the landmark Log-Rank test with the Z-OLS correction was applied¹³. It was checked that results were consistent with the tests at specific time point, but for brevity the p-values were not reported.
The main statistical analysis was made as an intention to treat (ITT) analysis, i.e. all patients enrolled contributed to the analysis of outcome since first auto (108 auto/RICallo, 249 auto). In addition, an exploratory analysis was conducted in two subgroups defined by the presence or absence of del(13). Outcomes were also compared after the second transplantation, including only patients who got the type of transplantation planned according to protocol (auto/RICallo: 92, auto/auto: 104).

**Results**

**Intention to treat (ITT) analysis of all patients**

The results of the ITT analysis are shown in Figures 1-3. The PFS was significantly better for the auto/RICallo group being 33% versus 18% (p=0.003) at 60 months and 22% versus 12% (p=0.027) at 96 months. This benefit for the auto/RICallo group was emerging after two to three years of follow-up and was related to a significantly lower relapse risk, which was 52% and 60% versus 77% and 82% at 60 and 96 months (overall p=0.0002) in the auto/RICallo and auto groups respectively. Similarly, OS was significantly superior in the auto/RICallo group, being 64% and 49% at 60 and 96 months respectively, versus 57% (p=0.204) and 36% (p=0.030) in the auto group. NRM was significantly higher in the auto/RICallo group, being 13% at 36 months, as compared to 3% in the auto group (p=0.0001). This difference did not increase significantly with time, being 18% versus 6% at 96 months. The CR rate was similar at 12 months, 34% versus 36%, but tended to increase in the auto/RICallo group and was 50% versus 41% at 60 months. For patients who did not obtain CR, the best response status in the auto/RICallo and auto group were partial remission (PR) 43% versus 50%, no response 3% versus 5%, and progressive disease 3% versus 4%, respectively.

**Analysis of deletion (13) status**

Considering first patients with the del(13) abnormality, PFS was 31% and 21% versus 10% and 5% at 60 (p=0.016) and 96 months (p=0.026) in the auto/RICallo and auto groups, respectively (Fig. 4). Without the del(13) abnormality the PFS was 41% and 26%, versus 23% and 16% at 60 months (p=0.054) and 96 months (p=0.198) in the auto/RICallo and auto
groups, respectively. The advantage for auto/RICallo tended to be more pronounced in patients with the del(13) abnormality, but was also seen in patients without the del(13). Thus, the prognostic impact on PFS of the chromosome del(13) abnormality tended to be more pronounced in the auto group (i.e. 5 % versus 16 % PFS in patients with and without the del(13) abnormality at 96 months (p= 0.004)) in contrast to the auto/RICallo group (i.e. 21% versus 26% PFS in patients with and without the del(13) abnormality at 96 months (p= 0.490)). A similar difference in impact on OS was seen, being more pronounced in the auto group i.e. 31 % versus 46% in patients with and without the del(13) abnormality at 96 months (p=0.055) than in the autoRIC/allo group (i.e. 47% versus 55% OS in patients with and without the del(13) abnormality at 96 months (p=0.686)). Thus, here too the impact of del(13) seems to have more importance as a poor prognostic factor in the auto than in the auto/RICallo group, indicating that to some extent allogeneic in contrast to autologous transplantation may overcome a poor prognostic parameter like del(13).

Analysis of patients receiving auto/RICallo versus tandem auto/auto according to protocol

The advantage of auto/RICallo, including only those patients who received the RICallo according to protocol, as compared to auto/auto, including only those patients who received this modality in a planned tandem fashion, was similar to that observed in the ITT analysis (Figs 5-6). The PFS from second transplant was 37 % and 24 % versus 22 % and 12 % at 60 (p=0.023) and 96 months (p=0.060) in the RIC/allo and auto/auto groups, respectively (Fig 5). Thus, the tandem auto/RICallo group tended to be even better considering that the PFS time was now calculated from the time of second transplant. The difference in OS between tandem auto/RICallo and tandem auto was similar as in the ITT analysis. OS was 64 % and 52 % versus 61 % and 35 % at 60 (p= 0.608) and 96 months (p=0.027) in the auto/RICallo versus auto/auto, respectively (Fig 6). The RL and NRM were similar to the ITT analysis. Non-relapse mortality was 12 % versus 2 % at 24 months (p=0.003) and the relapse rate was 56 % versus 82 % at 96 months (p=0.001).

Overall survival from disease progression

At the time of follow up 64 patients in the auto/RICallo group and 205 patients in the auto group had progressed. On an ITT analysis OS at 60 months from progression was 50% in the
auto/RICallo group and 27% in the auto group (p=0.003) (Fig 7). Comparing only those patients that had received auto/RICallo (n=51) or auto/auto (n= 84) according to protocol the corresponding figures at 60 months were 48% and 26% (p=0.019) (Fig 5). Out of the 16 patients in the auto/RICallo group receiving DLI after progression, 7 responded; 4 entered CR and 3 PR. Out of the 4 patients that entered CR, 2 were still in CR at follow-up at 87 and 125 months, while 2 died at 86 and 93 months after inclusion. Out of the 3 patients entering PR, 2 were still in PR at follow-up at 84 and 108 months and one patient entered CR after a second RICallo and was alive at 101 months.

Graft-versus-host disease

Acute GVHD in 92 patients who received tandem RICallo was as previously described, i.e. grade I in 11 %, grade II in 9 %, grade III in 9% and grade IV in 2 %. Sixty-seven % of patients had no acute GVHD. Fifty-four per cent of the patients developed chronic GVHD, which was limited in 31% and extensive in 23%. As previously described, patients with acute GVHD had a higher NRM. The cumulative NRM at 60 months in patients with or without acute GVHD was 36 % versus 4 % (p<0.001). In a landmark analysis from 12 months there were no significant differences in OS, PFS, relapse incidence or NRM between patients with or without chronic GVHD that occurred within the first 12 months.
Discussion

The importance of long-term follow-up for the correct evaluation of auto/RICallo versus auto is clearly demonstrated in this study. The additional 35 months of follow-up of the NMAM2000 study in comparison to our previous presentation of the study\(^8\) shows that nearly twice as many patients are progression-free after 8 years with the auto/RICallo procedure compared to the auto procedure (22\% versus 12\%) and 49\% are surviving after the auto/RICallo procedure compared to 36\% with auto at this time. In patients who actually received the auto/ RICallo transplant according to protocol and compared to those who received two auto transplants in a planned approach the differences were similar. Thus our long term results show superiority for the auto/RICallo procedure irrespective of whether the data were analyzed on an intention to treat basis or according to protocol.

The study also shows that patients with or without the del(13) abnormality had similar outcome when treated with auto/RICallo and better than with auto, in contrast to the outcome with auto, which was poorer in patients with the del(13) abnormality than in those without, corroborating with other studies\(^9,10\). Although it is now known that del(13) is not a prognostic marker by itself it is frequently associated with other more important prognostic chromosomal markers like del(17p), t(4;14) and t(14;16). Therefore, most studies analyzing only del(13) show that patients with the aberration tends to have poorer prognosis than those without\(^9,10\) – as in our study. This adds to evidence indicating that del(13) is a surrogate marker for other chromosomal aberrations indicating poor prognosis with auto. Our results suggest that allogeneic transplantation may overcome this poor prognosis following autologous transplantation corroborating with recent retrospective findings\(^14\).

An interesting observation is that despite the fact that a variety of treatments was administered following progression, OS after relapse/progression was significantly superior in the auto/RICallo group. The previously well documented graft versus myeloma effect\(^15,16\) may persist in patients after auto/RICallo at progression and contribute to this difference. The use of DLI in a fraction of auto/RICallo patients may also play a role. The difference in clinical outcome was seen despite a higher frequency of additional autologous transplants performed in the auto group, while the effect of a difference in the use of new drugs could not be adequately analyzed.
Out of three prospective studies\textsuperscript{1-3} with somewhat different trial designs published before our first report of the NMAM2000 study two supported the better outcome with auto/RICallo as compared to tandem auto as discussed previously\textsuperscript{2,3}. Since then two additional studies including large numbers of patients have been published, i.e. the BMT CTN 0102 study\textsuperscript{5}, and the HOVON-50 study\textsuperscript{4}. At a first glance, both seem to contradict our results.

However, the BMT CTN study had significantly shorter follow-up time. Endpoints were PFS and OS at 36 months. At this time results are comparable to ours, i.e. OS was 77 \% with auto RICallo and 80 \% with auto/auto in the BMT CTN study as compared to 71 \% versus 68 \% respectively in our study. PFS with auto/RICallo at this time is exactly the same in the two studies, i.e. 43 \%, while the auto/auto procedure in the BMT CTN study tends to be somewhat better, i.e. 46 \% versus 39 \% in our study. The non-relapsed mortality was similar in the two groups, i.e. 13 \% in our study versus 11 \% in the BMT CTN study with the auto/RICallo procedure and 3 \% versus 4 \% with auto/auto respectively. Thus up to 36 months our results are similar to those of the BMT CTN study, but our longer follow-up clearly demonstrated the advantage of auto/RICallo.

The HOVON study\textsuperscript{4} had a somewhat different approach using conditioning with TBI 2Gy without fludarabine and maintenance therapy with thalidomide in some of the auto patients. OS at 6 years was 55 \% in patients with or without a donor, as compared 59 \% after auto/RICallo and 49 \% after auto/auto in our study. However PFS at 6 years was 28 \% in patients with a donor, compared to 22 \% without a donor in the HOVON study. The corresponding figures in our study were 30 \% and 16 \%. Although not significant in the HOVON study, while it was in ours, the tendency seems to be the same, corroborating with a significantly lower relapse/progression rate in the auto/RICallo arm in both studies. Thus the main difference between the two studies seems to be the better outcome with the auto/auto procedure in the HOVON study. Patient selection or treatment differences could play a role. In the HOVON study nearly half of the patients had a sibling donor, while this usually only is the case in about one third. Although there was no significant difference in prognostic parameters at diagnosis, there were a few more patients in CR or very good PR at inclusion (40\% versus 36\%) and fewer patients with the del(13) abnormality assessed by FISH (13\% versus 21\%) in the no donor group, these minor differences seem insufficient to be responsible for the better results in the auto group compared to ours. Although it was not
proven to be effective, a fraction of the auto patients received maintenance treatment with thalidomide contrary to our patients. Thus, although the authors claim no advantage for the auto/RICallo procedure, it has to be pointed out that the relapse and progression rate at 6 years was 77% in the auto group (79% in the NMAM 2000 study), and 55% in the auto/RICallo group (54% in the NMAM 2000 study) at six years. Here, the results seem to be practically identical and to the advantage of the auto/RICallo procedure.

Although our report and the Italian study indicate better outcome with the auto/RIC allo transplant procedure than with only auto transplantation and no study has shown worse outcome with the auto/RICallo approach, the early higher NRM and the risk of chronic GVHD has raised some editorials questioning the value of this treatment modality. Such results as well as our results indicating that certain high risk factors at diagnosis can be overcome by auto/RICallo may be reason to restrict studies on auto/RICallo to poor risk patients. It also appears that selection of donors could be improved. So far, prospective studies have been based on the availability of an HLA identical sibling donor. In a recent study it was shown that selection of donors with KIR haplotype B could significantly improve results.

A burning question is whether allogeneic transplants should be postponed until progression and relapse. This is not currently clear. The present study does not give an answer to this question. However, some other studies including a retrospective EBMT study in progress indicate that allogeneic transplantation might be an option. Still, these studies are not prospective, and do not compare results with those of new drug treatment or autologous transplantation. A recently published EBMT study showed very good results with the VTD (bortezomib + thalidomide+dexamethasone) combination following progression.

Our study was designed when the new drugs were not yet commonly used. Numerous studies have later proven their efficacy. Combinations of new drugs have been used for induction before autologous transplantation and recent studies have shown improved PFS and perhaps survival using maintenance therapy following autologous transplantation. However most of these studies have considerably shorter follow up than the median of 96 months in our study and long term survival can therefore not be adequately compared to our results with auto/RICallo. In one of the most recent studies using new drugs both for induction (bortezomib, lenalidomide and/or thalidomide) and prospectively lenalidomide for maintenance, including only patients responding to the autologous transplantation, results do
not appear superior to our results with autoRICallo at 4 years and long term results are lacking\textsuperscript{26}. Recently it has been shown that using bortezomib in association with allotransplantation may reduce GVHD without significantly hampering GVM\textsuperscript{29,30}. Also, lenalidomide appears to be very effective in treating relapse following allogeneic transplantation\textsuperscript{31}. Thus new drugs may be effectively used in combination with allotransplantation and improve results with this transplant modality even further.

Our conclusion is that the tandem auto/ RICallo transplantation modality is a promising therapeutic option for younger multiple myeloma patients with poor prognostic features. Here, the moderately higher early NRM may be acceptable, while it may be of less value to patients with good prognostic parameters, particularly when considering the improved treatment results currently available for new drugs like bortezomib, lenalidomide and others. However, it is also likely that combinations with these drugs and early allogeneic transplantation may even further improve the results of auto/RICallo transplants. Carefully designed studies with long follow-up need to be performed in both newly diagnosed and relapsed patients. Such studies may prove that allogeneic transplantation for myeloma should not be abandoned.
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Author contribution and conflict of interest

Gösta Gahrton: Designed the study, performed research and wrote the manuscript. No conflict of interest.

Simona Iacobelli: Participated in designing the study, performed the statistics and participated in writing the manuscript. No conflict of interest.

Bo Björkstrand: Participated in designing the study, performed research and participated in writing the manuscript. Presently employed by the Novartis Company. Employed by the Karolinska University Hospital during the design of the study and in the course of the patient inclusion.

Ute Hegenbart: Performed research and participated in writing the manuscript. No conflict of interest.

Astrid Gruber: Performed research and participated in writing the manuscript. No conflict of interest.

Hildegard Greinix: Performed research and participated in writing the manuscript. No conflict of interest.

Liisa Volin: Performed research and participated in writing the manuscript. No conflict of interest.

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Hartmut Goldschmidt: Performed research and participated in writing the manuscript. No conflict of interest.
Theo de Witte: Performed research and participated in writing the manuscript. No conflict of interest.
Curly Morris: Performed research and participated in writing the manuscript. No conflict of interest.
Dietger Niederwieser: Participated in designing the study, performed research and participated in writing the manuscript. No conflict of interest.
Laurent Garderet: Performed research and participated in writing the manuscript. No conflict of interest.
Nicolaus Kröger: Performed research and participated in writing the manuscript. No conflict of interest.
References


Legends to Figures

Figure 1. Progression free survival (PFS) in patients with Multiple Myeloma treated with auto/RIC allo or auto alone. PFS was significantly better for the auto/RIC allo group being 33% versus 18% (p=0.003) at 60 months and 22% versus 12% (p = 0.027) at 96 months. All patients included – intention to treat. Gray = auto/RIC allo; Black = auto.

Figure 2. Relapse/Progression rate (RL) in patients with Multiple Myeloma treated with auto/RIC allo or auto alone. RL was lower with auto/RIC allo, i.e. 52% versus 77% at 60 months and 60% versus 82% at 96 months in the auto/RIC allo and auto groups respectively (overall p= 0.0002) All patients included – intention to treat. Gray = auto/RIC allo; Black = auto.

Figure 3. Overall survival (OS) in patients with Multiple Myeloma treated with auto/RIC allo or auto alone. Overall survival was better in the auto/RIC allo group long term, being 49% versus 36% at 96 months in the auto/RIC allo and auto groups respectively (p= 0.030). All patients included – intention to treat. Gray = auto/RIC allo; Black = auto.

Figure 4. Progression free survival (PFS) in patients with Multiple Myeloma with the del(13) abnormality. Progression free survival was better with auto/RIC allo being 31% versus 10% (p=0.016) at 60 months and 21% versus 5% at 96 months (p=0.026). All patients with del(13) included – intention to treat. Red = auto/RIC allo; Black = auto.

Figure 5. Progression free survival (PFS) in patients with Multiple Myeloma receiving second transplant (RIC allo or second auto) according to protocol. Progression free survival was better with auto/RIC allo than with auto/auto being 37% versus 22% at 60 months (p=0.023) and 24% versus 12% at 96 months (p=0.060). Gray = auto/RIC allo; Black = auto.

Figure 6. Overall survival (OS) in patients with Multiple Myeloma receiving second transplant (RIC allo or second auto) according to protocol. Overall survival was better with auto/RIC allo than with auto/auto being 64% versus 61% at 60 months (p=0.608) and 52% versus 35% at 96 months (p=0.027). Gray = auto/RIC allo; Black = auto.

Figure 7. Overall survival (OS) from the time of first relapse/progression in patients with Multiple Myeloma treated with auto/RIC allo or auto alone. The survival from first relapse/progression was significantly longer in the auto/RIC allo arm than in the auto arm being 50% with auto/RIC allo versus 27% with auto at 60 months from progression (p= 0.003). All patients that reached first relapse/progression included. Gray = auto/RIC allo; Black = auto.
Figure 1

Relapse/Progression–Free Survival from 1st transplant

Intention to treat

- Auto
- Auto/RICallo

$p=0.027$

Time since 1st auto (months):

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Figure 2

Relapse/Progression Incidence from 1st transplant

Intention to treat

- Auto
- Auto/RICallo

\[ p = 0.0002 \]

time since 1st auto (months)

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<th>Time (months)</th>
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<th>Auto/RICallo 108</th>
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<td>40</td>
<td>32</td>
</tr>
<tr>
<td>84</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>96</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>108</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 3

Overall Survival from 1st transplant

Intention to treat

- Auto
- Auto/RICallo

p=0.030

time since 1st auto (months)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Auto</th>
<th>Auto/RICallo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>249</td>
<td>108</td>
</tr>
<tr>
<td>12</td>
<td>232</td>
<td>98</td>
</tr>
<tr>
<td>24</td>
<td>207</td>
<td>85</td>
</tr>
<tr>
<td>36</td>
<td>170</td>
<td>77</td>
</tr>
<tr>
<td>48</td>
<td>153</td>
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<td>60</td>
<td>140</td>
<td>69</td>
</tr>
<tr>
<td>72</td>
<td>122</td>
<td>63</td>
</tr>
<tr>
<td>84</td>
<td>95</td>
<td>54</td>
</tr>
<tr>
<td>96</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>108</td>
<td>16</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 4

Relapse/Progression–Free Survival from 1st transplant

Patients with del(q13)

- Auto
- Auto/RICallo

p=0.026

time since 1st auto (months)

<table>
<thead>
<tr>
<th>Auto</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto/RICallo</td>
<td>29</td>
<td>21</td>
<td>17</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 5

Relapse/Progression-Free Survival after 2nd transplant

- Auto/Auto
- Auto/RICallo

p=0.060

Time since 2nd trx (months)

Auto/Auto: 104, 80, 57, 43, 29, 23, 18, 13
Auto/RICallo: 92, 62, 50, 41, 34, 34, 26, 18
Figure 6

Overall Survival after 2nd transplant

- Auto/Auto
- Auto/RICallo

p=0.027

time since 2nd trx(months)

<table>
<thead>
<tr>
<th></th>
<th>Auto/Auto</th>
<th>Auto/RICallo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>104</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>24</td>
<td>86</td>
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<td>36</td>
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<td>48</td>
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<td>72</td>
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<td>53</td>
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<tr>
<td>84</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>96</td>
<td>17</td>
<td>21</td>
</tr>
</tbody>
</table>
Figure 7

Overall Survival from first progression

- **Auto**
- **Auto/RICallo**

**p=0.003**

Time since 1st progression (months)

<table>
<thead>
<tr>
<th>Auto</th>
<th>205</th>
<th>150</th>
<th>114</th>
<th>88</th>
<th>50</th>
<th>31</th>
<th>16</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto/RICallo</td>
<td>64</td>
<td>49</td>
<td>39</td>
<td>35</td>
<td>28</td>
<td>22</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>
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