Prognostic Factors for Post-Relapse Survival after ex-vivo CD34+-Selected (T cell-depleted) Allogeneic Hematopoietic Cell Transplantation in Multiple Myeloma

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Abstract

Background—Allogeneic hematopoietic cell transplantation (alloHCT) for multiple myeloma (MM), with its underlying graft-versus-tumor capacity, is a potentially curative approach for high-risk patients. Relapse is the main cause of treatment failure, but predictors for post-relapse survival are not well-characterized.

Methods—Retrospective analysis to evaluate predictors for post-relapse overall survival (OS) in 60 MM patients who progressed after myeloablative T cell-depleted alloHCT.

Results—Median age was 56 years, and 82% had high-risk cytogenetics. Patients received a median of 4 lines of therapy pre-HCT, with 88% achieving at least a partial response (PR) prior to alloHCT. Of the 38% who received a preemptive post-HCT therapy, 13 received donor lymphocyte
infusions (DLI) while 10 received other interventions. Relapse was defined as very early (<6 months, 28%), early (6–24 months, 50%), or late (>24 months, 22%). At relapse, 27% presented with extramedullary disease. Median post-relapse OS by time-to-relapse was 4 months, 17 months, and 72 months, for patients in the very early, early, and late relapse groups, respectively (p=0.002). Older age, relapse with extramedullary disease, <PR prior to alloHCT, <PR by day +100, and no maintenance were prognostic for inferior post-relapse OS on univariate analysis. On multivariate analysis adjusted for age and sex, very early relapse [HR 4.37 (95%CI 1.42–13.5)], relapse with extramedullary disease [HR 5.20 (95%CI 2.10–12.9), and DLI for relapse prevention [HR 0.11 (95%CI 2.10–12.9)] were significant predictors for post-relapse survival.

Conclusion—Despite their shared inherent high-risk status, MM patients have significantly disparate post-HCT relapse courses, with some demonstrating long-term survival despite relapse.

Keywords
multiple myeloma; allogeneic hematopoietic stem cell transplantation; relapse; donor lymphocyte infusion; T cell depletion; CD34+ selection

INTRODUCTION

Despite numerous therapeutic advances and improved clinical outcomes for multiple myeloma (MM) over the past two decades, the disease remains largely incurable. Allogeneic hematopoietic stem cell transplantation (alloHCT), defined by its unique underlying graft-versus-MM effect, offers immune-mediated curative potential. Several large registry and single-center retrospective studies, including a meta-analysis of pooled data and a meta-analysis of pooled-individual data, support the concept that modern alloHCT strategies can extend relapse-free survival, overcome the poor prognosis of high-risk cytogenetics with acceptable toxicity, and synergize with post-relapse therapy.

We previously reported our experience using an ex vivo CD34+-selected (T cell-depleted) alloHCT platform for high-risk MM, and showed long-term disease control for some patients with 1- and 3-year progression-free survival of 53% and 30%, and 1- and 3-year overall survival (OS) of 70% and 50%. Most important, the rate of non-relapse mortality was lower than prior reports of non-T cell-depleted alloHCT (22% vs ~30–40%) and similar to alloHCT for other diseases. In addition, there was low cumulative risk of graft-versus-host disease (GvHD) (7% acute GvHD by day 100 and 8% chronic GvHD by 1 year). Relapse, however, continues to be the primary cause of treatment failure (25% by 1 year and up to 47% by 3 years), but there are no prognostic tools to assess the post-relapse course for this unique, high-risk patient population.

In this study, we aimed to define differential patterns and predictors of post-relapse survival for patients who relapsed or progressed after a T cell-depleted alloHCT for MM.
METHODS

Patient Population

This was a single-center retrospective cohort study. Study subjects included all consecutive adult patients with MM who underwent a T cell-depleted alloHCT at Memorial Sloan Kettering Cancer Center between January 2010 to December 2017 and experienced relapse or progression after alloHCT. Patients were treated under 3 prospective protocols (NCT01119066, NCT01131169, NCT01758328) or per standard treatment plan. All patients received a uniform myeloablative chemotherapy-only conditioning regimen and a T cell-depleted peripheral blood stem cell graft. Patients on NCT01131169 and NCT01758328 were intended to receive a donor lymphocyte infusion (DLI) or Wilms tumor 1 (WT1)-specific donor-derived cytotoxic T cells for relapse prevention, respectively. In all protocols, maintenance or additional relapse prevention strategies, including DLI, was administered at the discretion of the treating physician. Written informed consent for treatment was obtained from all patients and donors. Approval for this retrospective review was obtained from the Institutional Review and Privacy Board.

Donors, Conditioning Regimen, and Allografts—Donors were related or unrelated and were all either HLA-matched or had a single antigen/allele mismatched at HLA-A, -B, -C, -DRB1, or -DQB1 loci. The preparative regimen comprised myeloablative doses of intravenous (i.v.) busulfan at 0.8 mg/kg/dose every 6 hours for 10 total doses on days −9 to −7, i.v. melphalan 70 mg/m²/day on days −7 and −6, and i.v. fludarabine 25 mg/m²/day on days −6 to −2. Busulfan and melphalan doses were adjusted to ideal body weight for patients weighing >125% of ideal body weight. After the initial dose, subsequent busulfan doses were adjusted based on first-dose pharmacokinetics. On days −3 and −2, rabbit antithymocyte globulin was administered at 2.5 mg/kg/day, along with methylprednisolone at 2 mg/kg/day. Grafts were depleted of T cells by ex vivo positive CD34+ selection using the CliniMACS CD34 Reagent System (Miltenyi Biotech, Bergisch Gladbach, Germany). Patients did not receive planned pharmacologic immunosuppression after alloHCT unless required for the treatment of GvHD.

Patients on protocol NCT01131169 were eligible to receive DLI for relapse prevention or treatment of disease progression. Recipients of HLA-matched allografts received up to 3 doses of prophylactic DLI at 5×10^5 CD3+ cells/kg at 4 to 6 months after transplantation, followed 3 to 4 months later by a dose of 5×10^5 CD3+ cells/kg, and then 2 to 4 months later by a dose of 1×10^6 CD3+ cells/kg. Recipients of HLA-mismatched allografts received DLI only if trending toward or meeting criteria for disease progression or relapse, and no sooner than 4 to 6 months after transplantation, with a first dose of 1×10^5 CD3+ cells/kg, followed 1 to 3 months later by a second dose of 5×10^5 CD3+ cells/kg, and then 3 to 4 months later by a third dose of 1×10^6 CD3+ cells/kg. HLA-matched allograft recipients meeting criteria for progression or relapse were also eligible for DLI treatment under the same dosing schedule as mismatched graft recipients. DLI was not given to any patients with active or improving GvHD or with disease progression or relapse within 4 months of transplantation. Similar guidelines were used for patients receiving DLI off protocol.
**Relapse Criteria and Study Definitions**—Relapse was defined by the consensus recommendations of the International Myeloma Workshop as a 25% increase from baseline in the serum monoclonal protein (M-protein; absolute increase > 0.5 g/dl), urine M-protein (absolute increase >200 mg/day), percentage of bone marrow plasma cells (absolute percentage increase >10%), and/or the difference between involved and uninvolved free light chain levels (absolute increase >10 mg/dl)\(^{15}\), or by the presence of definite new bone lesions and/or soft tissue plasmacytomas, with a clear increase in the size of existing plasmacytomas, or hypercalcemia not attributed to another cause\(^{16}\). Refractory MM was defined as disease failing to achieve at least a minimal response to therapy\(^ {15,17}\).

Clinical patterns of relapse were categorized as symptomatic MM (any relapse criteria with associated symptoms or related organ dysfunction), biochemical relapse (with no associated symptoms or related organ dysfunction), or any criteria for progression with extramedullary disease (para-skeletal or organ involvement or transformation to plasma cell leukemia)\(^ {15}\).

Acute and chronic GvHD diagnosis and grading was according to established criteria\(^ {18,19}\). High-risk cytogenetics classification required the presence of any of the following: gain 1q, deletion 17p, deletion 13, complex cytogenetics, t(4;14), or t(14;16) detected by fluorescence in situ hybridization analyses or karyotype\(^ {20}\).

**Outcomes and Statistical Analysis**—The primary outcome was the post-relapse survival for MM patients, measured from the time of relapse or progression after alloHCT until the date of death, categorized by time-to-relapse as follows: very early (<6 months), early (6–24 months), and late (>24 months). The secondary objectives were to identify other predictors of post-relapse survival.

All nominal and continuous characteristics were summarized using descriptive statistics. We compared groups using chi-squared and Fisher’s exact tests for categorical variables and Mann-Whitney tests for continuous variables. Survival curves were estimated using the Kaplan-Meier method, with group comparison by the log-rank test. Prognostic factors for OS after relapse were included in a multivariable Cox proportional hazard model that included sex, age, and variables significantly (P < .05) associated with OS in univariable analysis, excluding variables inducing excessive multicollinearity. All analyses were conducted using R version 3.5.1.

**RESULTS**

**Baseline Characteristics**

Between January 2010 to December 2017, 114 MM patients underwent an alloHCT, among whom 60 patients (53%) relapsed or had progression of disease and comprised the study population. Patient, disease, and alloHCT characteristics are shown in Table 1.

The median age at alloHCT was 56 years (36–66). The median prior lines of therapy was 4 (1–10). All patients had a previous autologous HCT, and 22 (37%) received two autologous HCT. Fifty-three patients (88%) had at least a partial response (PR) prior to alloHCT. Seven patients (12%) were transplanted with refractory/progressive disease.
Seven patients (12%) had a history of grade I (n=3) or grade II (n=4) acute GvHD prior to relapse. Median onset of acute GvHD was 49 days post-transplant (21–87 days). No patients developed chronic GvHD.

**Relapse Prevention strategies**

Table 2 lists the maintenance/preemptive strategies by best response post-alloHCT. Thirty-seven (62%) patients relapsed without receiving post-alloHCT maintenance/preemptive strategies. Thirteen patients (22%) received at least one DLI alone or in combination with proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), or other therapies for relapse prevention (8 patients under protocol NCT01131169 and 5 patients per treating physician recommendation). Of these, 6 were in CR/sCR, 5 in VGPR, and 2 in PR after alloHCT. Four patients had prior acute GvHD that was quiescent and only one had recurrent symptoms after DLI (grade I skin and grade II gut). Four additional patients had new onset GvHD after DLI (2 grade I skin and 2 grade II gut).

**Relapse Presentation**

The median time-to-relapse was 12 months (range 1–95 months). Seventeen (28%), 30 (50%), and 13 patients (22%) relapsed very early (< 6 months), early (6–24 months), and late (>24 months) post-HCT, respectively. Thirty (50%), 14 (23%), and 16 patients (27%) presented with biochemical relapse, symptomatic MM with no evidence of extramedullary disease, and with extramedullary disease, the latter of which included 15 patients with para-skeletal or organ involvement and one patient with transformation to plasma cell leukemia. Seven of the 15 patients with extramedullary disease at relapse had prior evidence of extramedullary disease before alloHCT, including 2 with evidence of treatment response and 5 with active extramedullary lesions at the time of alloHCT.

Chimerism analysis at the time of relapse was available for 53 patients. Twenty-two (42%) relapsed with persistent 100% donor chimerism (12 with biochemical relapse, 3 with symptomatic MM with no evidence of extramedullary disease, and 7 with evidence of extramedullary disease), 6 (11%) with ≤5% recipient chimerism, and 24 patients (45%) with >5% recipient chimerism.

**Post-relapse OS**

The median follow-up after relapse among surviving patients was 18 months (range 1–77). The median post-relapse OS for the entire cohort was 17 months (95% CI 9–31), and the median post-relapse OS by time-to-relapse was 4 months (95% CI 1–6), 17 months (95% CI 8–NR), and 72 months (95% CI 17-NR) for patients relapsing very early, early, and late, respectively (p=0.002) (Figure 1).

On univariable analysis (Table 3), factors associated with poorer post-relapse OS were relapse with extramedullary disease [2mo (95% CI 1–5) vs 21mo (95% CI 16-NR), p<0.0001]; older age [<50 yr: 46mo (95% CI 26-NR), 50–59yr: 13mo (95% CI 5–21), 60 yr: 5mo (95% CI 2-NR), p=0.006]; stable disease (SD)/progressive disease (PD) prior to HCT compared with ≥ partial response (PR) [3mo (95% CI 1-NR) vs 17mo (95% CI 13-NR), p<0.001], SD/PD at day 100 post- HCT compared with ≥PR [1mo (95% CI 1-NR) vs 17mo
(95% CI 11-NR), p=0.02]; and no maintenance post alloHCT compared with maintenance/preemptive other than DLI, and DLI for relapse prevention [8 mo (95% CI 4–14) vs 21mo (95% CI 4-NR) vs not reached (95% CI NR-NR), respectively, p=<0.001].

On multivariate analysis (Table 3) after adjusting for age and sex, very early relapse [HR 4.37 (95% CI 1.42–13.5)], relapse with extramedullary disease [HR 5.20 (95% CI 2.10–12.9)], and DLI for relapse prevention [HR 0.11 (95% CI 2.10–12.9)] were significant predictors for post-relapse survival.

**Post-relapse treatment**

Fifty-three patients (88%) received additional therapy after relapse. Of the remaining patients, 5 patients died prior to therapy (4 relapsed with extramedullary involvement), one patient with biochemical relapse remains on expectant management, and one patient was lost to follow-up. Therapy after relapse is summarized in Table 4. Median lines of salvage therapy post-allo HCT relapse was 2 (range 1–8). Twenty patients received DLI for treatment of relapse, including 18 as part of initial salvage strategy. Eight of 18 received DLI alone, with an overall response rate (ORR) of 6 out of 8 (75%) achieving at least a PR, including 2 patients achieving a CR. For the 10 remaining patients, DLI was combined with lenalidomide (n=7), daratumumab and pomalidomide (n=2), and pembrolizumab (n=1); one patient achieved a CR, and the ORR was 4 out of 10 (40%). The remaining 2 patients received DLI in combination with third-line salvage therapy (DCEP and bendamustine-based regimen) with PR.

Four patients received a second alloHCT (median of 3.5 years after the first alloHCT and median of 5 lines of therapy between transplants), with three patients receiving reduced-intensity conditioning and one patient receiving the same myeloablative conditioning. Two patients died before day +100 of disease progression. One patient achieved a sCR that was sustained for 2 years prior to death from GvHD. Another patient progressed 3 months after second alloHCT, achieved a CR with salvage venetoclax and DLI that lasted 9 months, then received ipilimumab with subsequent progression treated with daratumumab, pomalidomide, and DLI, and is currently in ongoing CR 2 years since second alloHCT.

**DISCUSSION**

This is the largest study evaluating predictors of post-relapse survival for MM patients relapsing after T cell-depleted alloHCT with uniform myeloablative conditioning. We found that despite their similar baseline high-risk status, patients have significantly different post-relapse courses, with some patients achieving long-term survival despite relapse. The key predictors of outcome from the time of relapse include time-to-relapse after alloHCT, receiving DLI prior to relapse, and the clinical features of relapse.

Similar to relapse characteristics after autologous HCT, differences in time-to-relapse or progression after alloHCT define distinct post-relapse courses21. In our study, despite myeloablative conditioning, 28% of patients relapsed very early after alloHCT (<6 months) with dismal post-relapse course (median post-relapse OS of 4 months). Forty percent of patients in the very early relapse group achieved less than a PR at the time of alloHCT,
supporting the theory that chemoresistance to the conditioning chemotherapy, rather than an inadequate graft-versus-MM effect, drives relapse in this subpopulation of patients. In contrast, for the 22% of patients who had late relapse after alloHCT (>24 months), the median post-relapse OS was 6 years, suggesting different underlying disease biology and host/donor characteristics affecting the graft-versus-MM effect. The differences in post-relapse survival associated with time-to-relapse have been corroborated in studies evaluating predictors after unmodified alloHCT. Lopez-Corral et al, reported on 75 patients who relapsed or progressed after alloHCT (majority with reduced intensity conditioning) and showed the median OS for patients relapsing within 6 months was 11 months versus 120 months for those relapsing at a later time point.

The beneficial role of an underlying graft-versus-MM effect persisting after relapse has been supported by two observations. The first is that there is superior post-relapse OS in patients who relapse after sequential autologous-allogeneic HCT as upfront therapy compared with patients who relapse after tandem autologous HCT. A retrospective CIBMTR study by Htut and colleagues reported a long-term post-relapse survival advantage in the autologous/allogeneic HCT group starting at 12 months post-relapse despite an increased proportion of high-risk patients (HR for death in tandem vs autologous/allogeneic=1.55; P = 0.005). Similarly, the Blood and Marrow Transplant Clinical Trials Network 0102 Trial showed improved post-relapse survival for patients with standard-risk cytogenetics who relapsed after upfront autologous/allogeneic HCT versus tandem HCT. The second observation is that DLI induces complete remissions in patients with relapsed MM after alloHCT, which was evident in our study.

Studies of preemptive/maintenance cellular immunotherapy, either with DLI or donor-derived antigen-specific T cells, following T cell-depleted alloHCT to improve PFS and decrease relapse have been conducted for different diseases, with a key observation that the low incidence of GvHD after a T cell-depleted alloHCT does not compromise the graft-versus-tumor effect and facilitates further treatments after relapse. In our study, patients who received a planned DLI for relapse prevention after T cell-depleted alloHCT but then relapsed had superior survival after relapse than patients who received other therapies for maintenance/preemptive therapy or no therapy. The underlying mechanism, while unknown, is compelling and suggests a role of donor-derived antitumor immunity before relapse that persists after relapse. Mechanistic studies of DLI in MM show varied immune responses involving changes in T-cell populations, B cell expansion with antibody responses against MM-associated antigens, and NK responses. Extended post-relapse responses to salvage therapy after alloHCT may reflect synergy between the residual graft-versus-MM effect and the salvage therapy administered. Studies using maintenance lenalidomide after alloHCT have shown induction of both NK cell and T cell-mediated anti-MM activity and reconstitution of donor immune homeostasis. There have also been reports of potentiation of the effect of DLI when combined with PIs and IMiDs. In a study by Kroger et al., patients who only achieved a PR after alloHCT received preemptive DLI to deepen the response. If a CR was not achieved, patients received thalidomide or bortezomib. With DLI, 27% patients upgraded to CR, which further improved to 59% with the addition of thalidomide or bortezomib.
Relapse with extramedullary involvement has been reported in up to 20–35% of MM patients after alloHCT\textsuperscript{40–43}, which is consistent with our experience of 27% incidence using a T cell-depleted platform. While prior reports have not consistently demonstrated an impact of extramedullary disease on post-relapse survival, a recent report of daratumumab administration in this setting showed greater ORR for patients without extramedullary disease (70%) than with extramedullary disease (28\%).\textsuperscript{44} Consistent with this, patients with extramedullary involvement had poorer responses to salvage therapy in our study cohort (HR 5.20 for increased risk of death), and 25\% of these patients died soon after relapse without salvage therapy. Patients with extramedullary relapse continue to represent an unmet need in the field with a high risk of rapid deterioration and would benefit from clinical trials allowing inclusion of these patients.

The high rate of extramedullary relapses also limits the predictive value of serial chimerism analysis for detecting relapse after alloHCT for MM, as persistence of 100\% donor chimerism does not ensure absence of relapse risk\textsuperscript{43}. In our cohort, full donor chimerism was seen in 42\% of patients at the time of relapse and has been reported by others to be as high as 64\%.\textsuperscript{43} Of patients who relapse with full donor chimerism, approximately a third have extramedullary involvement (29\% in our cohort and 33\% reported\textsuperscript{43}). For clinical practice, this underscores the importance of comprehensive restaging practices after alloHCT to identify relapses presenting with residual 100\% donor chimerism. On the other hand, for cases of declining donor chimerism after a T cell-depleted alloHCT, our findings support a DLI-based approach to mitigate relapse. Finally, in terms of post-relapse management, almost 90\% of the patients in our study received salvage therapy after relapse, with one-third receiving additional cellular therapy with DLI or donor-derived WT1-specific cytotoxic T cells. Due to the limited number of patients, patient heterogeneity after relapse, and the inherent limitations of assessing post-relapse interventions in a retrospective single-center analysis, we are unable to fully assess the effect of specific post-relapse interventions on response or survival.

In conclusion, our results demonstrate that a subset of MM patients achieve long-term post-relapse survival after T cell-depleted alloHCT. Key predictors of outcomes from the time of post-alloHCT relapse include time-to-relapse after alloHCT, receiving a DLI-based intervention prior to relapse, and the clinical features of relapse. Although the role and timing of alloHCT for MM is evolving in the current era of rapid drug development, alloHCT, including our platform of T cell-depletion with preemptive DLI maintenance, offers a viable therapeutic option for select patients with high-risk disease. Future research should prioritize comprehensive assessments in the post-relapse setting to identify mechanisms of relapse, including genomic and transcriptional changes and patterns of immune evasion, with the ultimate goal of developing strategies to boost antitumor immune reactivity in the post-alloHCT setting.

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Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

• **DJ Chung**: Research support for clinical trials from Genentech

• **PB Dahi**: She serves on the scientific advisory board of Kite – A Gilead Company

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| Highlights |
|-------------------|
| • Time-to-relapse after T cell-depleted HCT defines distinct post-relapse outcomes |
| • Relapse with extramedullary disease is common and associates with dismal prognosis |
| • Donor lymphocyte infusion for relapse prevention improves post-relapse survival |
Figure 1:
Post-relapse overall survival after alloHCT by (A) Time-to-relapse (B) Relapse Presentation (C) Maintenance/Preemptive strategies. Time 0 represents the time of relapse. Allogeneic hematopoietic stem cell transplantation (AlloHCT), extramedullary disease (EMD), donor lymphocyte infusion (DLI).
Table 1:
Baseline Patient, Disease and alloHCT Characteristics

| Characteristic                        | Relapsed pts (N=60) |
|---------------------------------------|---------------------|
| Median Age at HCT (range)             | 56 (35–66)          |
| Age 60 (%)                            | 14 (23%)            |
| Male (%)                              | 37 (62%)            |
| Race                                  |                     |
| White                                 | 47 (78%)            |
| Black                                 | 7 (12%)             |
| Other                                 | 6 (10%)             |
| KPS                                   |                     |
| 80                                    | 28 (46%)            |
| 90–100                                | 30 (50%)            |
| NA                                    | 2 (3%)              |
| Median Lines of tx (range)            | 4(1–10)             |
| 5 lines (%)                           | 19(32%)             |
| Prior Auto (%)                        | 60 (100%)           |
| 2nd Auto (%)                          | 22 (37%)            |
| 3rd Auto (%)                          | 1 (2%)              |
| Thalidomide-refractory               | 15 (25%)            |
| Lenalidomide-refractory              | 50 (83%)            |
| Bortezomib-refractory                | 42 (70%)            |
| Pomalidomide-refractory              | 12 (20%)            |
| Carfilzomib-refractory               | 13 (22%)            |
| Daratumumab-refractory               | 3 (5%)              |
| Pre-HCT response                      |                     |
| sCR, CR, VGPR and PR (%)             | 53 (88%)            |
| SD or PD (%)                          | 7 (12%)             |
| High Risk Cytogenetics (%)            |                     |
| Yes                                   | 49 (82%)            |
| CIBMTR Risk                          |                     |
| Low                                   | 13 (22%)            |
| High                                  | 47 (78%)            |
| HCT-CI                                |                     |
| 0–3                                   | 51 (85%)            |
| 4                                     | 9 (15%)             |
| Donor                                 |                     |
| MRD                                   | 20 (33%)            |
| MUD                                   | 21 (35%)            |
| MMUD                                  | 19 (32%)            |
| CMV status (patient/donor)            |                     |
| +/+                                   | 25 (42%)            |
|                      | Relapsed pts (N=60) |
|----------------------|---------------------|
| +/−                  | 12 (20%)            |
| −/+                  | 5 (8%)              |
| −/−                  | 18 (30%)            |

**Acute GvHD**

| Grade | Count (Percentage) |
|-------|--------------------|
| I     | 3 (5%)             |
| II    | 4 (7%)             |

**Year**

| Year     | Count (Percentage) |
|----------|--------------------|
| 2010–2013| 33 (55%)           |
| 2014–2017| 27 (45%)           |
Table 2:
Relapse prevention strategies according to best response post-alloHCT

| Type of maintenance/Preemptive strategy | Total N= 60 | sCR/CR n=30 | VGPR n=11 | PR n=15 | SD n=4 |
|----------------------------------------|------------|-------------|-----------|---------|-------|
| None                                   | 37 (62%)   | 21          | 4         | 10      | 2     |
| DLI alone                              | 8 (13%)    | 4           | 2         |         |       |
| DLI + IMiD/PI                          | 3 (5%)     | 1           | 2         |         |       |
| DLI + IMiD+ Pembrolizumab              | 1 (2%)     |             | 1         |         |       |
| DLI + WT1                              | 1 (2%)     |             |           |         |       |
| WT1                                    | 4 (7%)     | 1           |           | 2       | 1     |
| IMiD                                   | 5 (8%)     | 2           | 1         | 1       | 1     |
| Pembrolizumab                          | 1 (2%)     |             |           |         |       |
|                         | Univariable HR (95% CI) | p-value | Multivariable HR (95% CI) | p-value |
|-------------------------|-------------------------|---------|---------------------------|---------|
| Age                     | 1.08 (1.03–1.14)        | <0.001  | 1.04 (0.99–1.09)          | 0.13    |
| Sex                     |                         |         |                           |         |
| female                  | reference               |         | reference                 | 0.13    |
| male                    | 0.56 (0.29–1.08)        | 0.08    | 0.58 (0.29–1.17)          |         |
| KPS                     |                         |         |                           |         |
| 80                      | reference               | 0.2     |                           |         |
| 90–100                  | 0.61 (0.31–1.20)        |         |                           |         |
| High Risk CG            |                         |         |                           |         |
| no                      | reference               | 0.3     |                           |         |
| yes                     | 1.62 (0.67–3.90)        |         |                           |         |
| Lines prior to HCT      |                         |         |                           |         |
| 1–2                     | reference               | 0.2     |                           |         |
| 3–4                     | 1.18 (0.51–2.73)        |         |                           |         |
| ≥5                      | 2.12 (0.90–4.98)        |         |                           |         |
| Pre-HCT response        |                         |         |                           |         |
| SD/PD                   | reference               | 0.002   |                           |         |
| ≥PR                     | 0.18 (0.07–0.47)        |         |                           |         |
| Best post-HCT response  |                         |         |                           |         |
| SD/PD                   | reference               | 0.046   |                           |         |
| ≥PR                     | 0.29 (0.10–0.82)        |         |                           |         |
| Relapse prevention therapy |                         | 0.027   |                           |         |
| none                    | reference               |         | reference                 |         |
| DLI                     | 0.06 (0.01–0.44)        | 0.11    | (0.01–0.91)               | 0.04    |
| Other                   | 0.57 (0.24–1.32)        | 0.55    | (0.20–1.49)               | 0.2     |
| Time-to-relapse         |                         | 0.022   |                           |         |
| late                    | reference               |         | reference                 |         |
| early                   | 2.18 (0.81–5.90)        | 2.52    | (0.82–7.79)               | 0.11    |
| very early              | 5.25 (1.85–14.9)        | 4.37    | (1.42–13.5)               | 0.01    |
| Type of relapse         |                         | 0.001   |                            | 0.001   |
| No EMD                  | reference               |         | reference                 |         |
| EMD                     | 5.22 (2.54–10.8)        | 5.20    | (2.10–12.9)               |         |
| Year of HCT             |                         |         |                           |         |
| 2010–2013               | reference               | 0.5     |                           |         |
| 2014–2017               | 0.80 (0.40–1.58)        |         |                           |         |
| Months from Dx to HCT   | 1 (0.99–1.01)           | 0.8     |                           |         |
Table 4:
Salvage therapies used after relapse post allo-HCT

| Therapy exposure                  | N=60, (%) |
|----------------------------------|----------|
| Median Lines of therapy after relapse (range) | 2 (0–8) |
| 5 Lines                          | 11 (19)  |
| DLI                              | 20 (33)  |
| Lenalidomide                     | 34 (57)  |
| Carfilzomib                      | 26 (43)  |
| Pomalidomide                     | 14 (23)  |
| Daratumumab                      | 17 (28)  |
| Checkpoint inhibitor             | 3 (5)    |
| Intensive chemotherapy (DCEP, VD-PACE) | 10 (17) |
| Venetoclax                       | 3 (5)    |
| WT1 CTLs                         | 10 (17)  |
| Autologous transplant            | 3 (5)    |
| Second allogeneic transplant     | 4 (7)    |