Published in final edited form as:

Biol Blood Marrow Transplant. 2019 April ; 25(4): 683–688. doi:10.1016/j.bbmt.2018.12.141.

Revised-International Staging System (R-ISS) is Predictive and Prognostic for Early Relapse (<24 months) after Autologous Transplantation for Newly Diagnosed Multiple Myeloma (MM).

Sathish Gopalakrishnan[1], **Anita D'Souza**[2], **Emma Scott**[3], **Raphael Fraser**[2,4], **Omar Davila**[2], **Nina Shah**[5], **Robert Peter Gale**[6], **Rammurti Kamble**[7], **Miguel Angel Diaz**[8], **Hillard M. Lazarus**[9], **Bipin N. Savani**[10], **Gerhard C. Hildebrandt**[11], **Melhem Solh**[12], **Cesar O. Freytes**[13], **Cindy Lee**[14], **Robert A Kyle**[15], **Saad Z. Usmani**[16], **Siddhartha Ganguly**[17], **Amer Assal**, **Jesus Berdeja**[18,19], **Abraham S. Kanate**[20], **Binod Dhakal**[21], **Kenneth Meehan**[22], **Tamila Kindwall-Keller**[23], **Ayman Saad**[24], **Frederick Locke**[25], **Sachiko Seo**[26], **Taiga Nishihori**[25], **Usama Gergis**[27], **Cristina Gasparetto**[28], **Tomer Mark**[29], **Yago Nieto**[30], **Shaji Kumar**[15], and **Parameswaran Hari**[2]

[1]Health Science North, Sudbury, Ontario, Canada;

[2]CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI;

[3]Center for Hematologic Malignancies, The Knight Cancer Institute, Oregon Health and Science University, Portland, OR;

[4]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI;

[5]Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX;

[6]Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom;

[7]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX;

[8]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain;

[9]Seidman Cancer Center, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH;

[10]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN;

[11]Markey Cancer Center, University of Kentucky, Lexington, KY;

Corresponding author: Parameswaran Hari, MD, MS, Professor of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226.

[12]The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA;

[13]Texas Transplant Institute, San Antonio, TX;

[14]Royal Adelaide Hospital, Adelaide, SA, Australia;

[15]Mayo Clinic Rochester, Rochester, MN;

[16]Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute/Atrium Health, Charlotte, NC;

[17]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS;

[18]Columbia University Medical Center, New York, NY;

[19]Sarah Cannon BMT Program, Nashville, TN;

[20]Osborn Hematopoietic Malignancy and Transplantation Program, West Virginia University, Morgantown, WV;

[21]Medical College of Wisconsin, Milwaukee, WI;

[22]Dartmouth Hitchcock Medical Center, Lebanon, NH;

[23]Division of Hematology/Oncology, University of Virginia Health System, Charlottesville, VA;

[24]Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL;

[25]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL;

[26]Department of Hematology & Oncology, National Cancer Research Center East, Chiba, Japan;

[27]Hematolgic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY;

[28]Duke University Medical Center, Durham, NC;

[29]University of Colorado Hospital, Aurora, CO;

[30]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

The Revised International Staging System (R-ISS) combines ISS with genetic markers and lactate dehydrogenase, and can prognosticate newly diagnosed multiple myeloma (MM). Early relapse (<24 months) after upfront autologous hematopoietic cell transplantation (AHCT) strongly predicts inferior overall survival (OS). We examined the ability of R-ISS in predicting early relapse and its independent prognostic effect on post-relapse survival after an early relapse. Using the Center for International Blood and Marrow Transplant Research database, we identified MM patients receiving first AHCT within 18 months after diagnosis with available R-ISS stage at diagnosis (n= 628). Relative risks of relapse/progression, progression-free survival (PFS) and OS were calculated with R-ISS group as a predictor in multivariate analysis. Among early relapsers,

post-relapse survival was tested to identify factors affecting post-relapse OS. The cumulative incidence of early relapse was 23%, 39% and 50% for R-ISS I, R-ISS II and R-ISS III, respectively ($p < 0.001$). Shorter PFS and OS were seen with higher stage R-ISS. R-ISS was independently predictive for inferior post-relapse OS among early relapsers, as was the presence of ≥3 comorbidities and the use of ≥2 induction chemotherapy lines. R-ISS stage at diagnosis predicts early post-AHCT relapse and independently affects post-relapse survival among early relapsers.

Keywords

myeloma stage; post-relapse survival; transplant

Introduction

Novel anti-myeloma agents, including proteasome inhibitors and immunomodulatory drugs, incorporated into induction therapy before high-dose therapy and autologous hematopoietic cell transplant (AHCT) have significantly improved survival in multiple myeloma (MM) patients over the past two decades, as shown by randomized trials and retrospective series. (1,2) Nonetheless, responses to novel agents vary among various biological subgroups. (3) A clearer understanding of the important prognostic factors for survival can improve risk stratification and therapeutic decision-making.

Available evidence shows a strong association between pre-transplant depth of response and post-transplant progression-free survival (PFS) and overall survival (OS). (4,5) Despite achieving deep pre-AHCT responses, some patients relapse early and have very poor OS. (6,7) Similarly, data from the Arkansas group suggest that the loss of an established complete response in the first 3 years confers an inferior prognosis when compared with a lower level of response that is sustained over time. (8) Thus early relapse represents a dynamic high-risk marker that is unknown at diagnosis and available only during the natural course of disease evolution.

The revised International Staging System (R-ISS), proposed in 2015 as a more accurate prognostic model for newly diagnosed MM, incorporates ISS stage, serum lactate dehydrogenase (LDH) and high-risk cytogenetics assessed by interphase fluorescent *in-situ* hybridization (FISH). High-risk cytogenetic abnormalities defined as the presence of del(17p) and/or t(4;14) and/or t(14;16), or an elevated LDH above the upper limit of normal are risk factors that upstage patients in the R-ISS system. At a median follow-up of 46 months, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups; the 5-year PFS rates were 55%, 36%, and 24%, respectively. (9)

We analyzed the impact of R-ISS stage at diagnosis to predict early post-AHCT relapse (defined as relapse/progression within 24 months after AHCT) and the influence of the R-ISS stage on post-relapse survival using the Center for International Blood and Marrow Transplant Research (CIBMTR®) database.

Patients and methods

Data Sources

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin. It comprises a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on allogeneic and autologous hematopoietic cell transplantation. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) level and Comprehensive Report Form (CRF) level. The TED-level data is an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data submitted to the SCTOD (Stem Cell Therapeutic Outcomes Database). When a transplant is registered with the CIBMTR, a subset of patients are selected for the CRF level of data collection through a weighted randomization scheme. The CRF-level captures additional patient, disease and treatment-related data. TED and CRF level data are collected pre-transplant, 100 days and six months post-transplant, annually until year 6 post-transplant and biannually thereafter until death.

Patient selection

Patients with MM receiving an upfront AHCT defined as AHCT within 18 months after diagnosis, with melphalan conditioning following a novel agent-based induction, and transplanted between 2008 and 2014 were included in this analysis. Based on the availability of all components of the R-ISS schema, 628 patients were included. The same data set was used for a recently published CIBMTR analysis. (10)

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study population using the median value and range for continuous variables and the frequency and percentage for categorical variables. Group comparisons were done by Kruskall-Wallis test, chi-square test, and Fisher exact test. The endpoints of interest included disease response, progression-free survival (PFS), and OS after transplant. Transplant-related mortality (TRM) was defined as mortality after transplant in the absence of disease relapse or progression. Disease response and progression were assessed using the international Myeloma Working Group (IMWG) consensus criteria. (11) PFS was defined as the interval without progressive disease with patients alive and without progression/relapse censored at last follow-up. OS was defined as time interval from diagnosis or time of relapse (in the case of post relapse OS) till

death from any cause with survivors censored at last follow-up. Survival probabilities were calculated by using the Kaplan-Meier estimator with the variance estimated by Greenwood's formula. We also examined post-relapse survival from the date of relapse/progression in patients with documented relapse or myeloma progression occurring within 24 months of AHCT. Age, gender, Karnofsky score, R-ISS, HCT comorbidity index, clinical trial enrollment, novel versus non-novel induction treatment, lines of chemotherapy, disease status at transplant, time from diagnosis to transplant, year of transplant and melphalan conditioning dose were tested in multivariate analysis.

Results

Patient characteristics and treatment details are shown in table 1. More patients in R-ISS III cohort required more than 1 line of chemotherapy prior to AHCT (29% compared to 20% for R-ISS II and 15% for R-ISS I). Eighty seven percent of patients proceeded to AHCT within 12 months of diagnosis. Pre transplant disease status of ≥VGPR was similar across the R-ISS stages I,II and III at 49%,53% and 52%, respectively. Post-transplant maintenance was administered to 74, 68 and 70%, respectively, within each R-ISS stage cohort.

Univariate analysis for Relapse/Progression, PFS and OS (Table 2):

The incidence of relapse/progression was higher, and PFS/OS were inferior with higher R-ISS stage (table 2). The cumulative incidence of early relapse within 24 months of AHCT was 23% for R-ISS I, 39% for R-ISS II and 50% for R-ISS III groups ($p < 0.001$). Table 2 summarizes the survival data. 3-year PFS for R-ISS stages I, II and III were 64 (57–71), 47 (41–53) % and 32 (20–45) % ($p < 0.001$) respectively. The 3-year OS for R-ISS stages I, II and III were 88 (95% CI:83–93) %; 75 (95% CI:70–80)%; 56 (95% CI:43–69)% ($p<0.001$), respectively.

Multivariate analysis for OS and post-relapse survival for early relapses:

Multivariate analysis showed that R-ISS III at diagnosis was independently prognostic for both OS from transplant (Table 3) and post-relapse survival in early relapses (table 4). Higher R-ISS stage; HCT-comorbidity index of ≥3 and ≥2 lines of pre-ASCT chemotherapy and relapse after full dose melphalan conditioning with 200 mg/m2 dose were significant factors associated with shorter OS overall. While treatment era (2008–2011 vs 2012–2014) was a significant prognostic factor for OS in the whole cohort, it was not significant for survival in the early relapse cohort. Figure 1 shows post-relapse survival by R-ISS groups. Median post relapse survival after an early relapse was 4.1 years, 2.5 years and 1.5 years for R-ISS I,II and III at diagnosis respectively.

Impact of Maintenance therapy:

Intent to post-transplant maintenance therapy was reported in 74, 68 and 70% of R-ISS I, II and III patients, respectively (Table 1). Comparison of survival after early relapse between those who received maintenance and no maintenance (table 5) indicated that there was no difference in survival after early relapse regardless of utilization of maintenance post AHCT($p=0.86$). The median time to relapse post transplant was similar in the maintenance and no maintenance arms. As our analysis was specifically looking at impact of maintenance

in post relapse OS, this manuscript does not report on response or rate of relapse in the maintenance vs no maintenance cohorts. Likewise, as all maintenance strategies were taken together, impact of proteasome inhibitors vs immunomodulatory agents in maintenance is not included in this analysis.

Discussion

In this contemporaneous CIBMTR study, we make the following clinically important observations: 1) R-ISS stage group predicts for early relapse after an upfront AHCT; 2) R-ISS independently predicts for post-relapse survival among those relapsing early; 3) in addition to R-ISS, higher HCT-CI, number of lines of induction chemotherapy pre-AHCT and relapse after standard dose melphalan when compared to lower dose of melphalan, were associated with inferior post-relapse survival among early relapse patients and 4) maintenance treatment did not impact post-relapse survival among early relapsers.

Early relapse defined as relapse within 24 months after AHCT for newly diagnosed MM remains an area of therapeutic challenge even in the modern era of myeloma. While high risk cytogenetics and depth of response post AHCT have been identified as high risk for early relapse, (12) these alone have not been able to characterize the group of patients who have high-risk MM. We, and others, have shown that early relapse post-AHCT is an important prognostic factor determining survival. (6, 12) In this current analysis, we found that despite achievement of deep responses pre-AHCT (approximately 50% of patients achieve ≥VGPR status pre-AHCT), a significant proportion of patients in all R-ISS stages (23% stage I; 39% stage II; 50% stage III) relapse in under 24 months. A recent CIBMTR analysis studying early relapse during three different time periods found that the incidence of early relapse has remained unchanged at ~ 35% between 2001–2004,2005–2008 and 2009–2013 (13) in spite of more patients receiving planned maintenance (72% compared to 6%) between the 2009–2013 and 2001–2004 period. The apparent constancy in the incidence of early relapse despite widespread adoption of novel agents and early AHCT is consistent with the notion that the majority of the benefit from novel agents for MM has accrued to biologically standard risk patients. (14–16) This also means that our current armamentarium for frontline management of myeloma does not address the innate biological features that contribute toward early relapse. Prospective trials of monoclonal antibodies such as daratumumab or elotuzumab added to triplet regimens are ongoing and it remains to be seen whether they can reduce the incidence of early relapse. (17–20)

In addition to R-ISS, HCT-CI >2, receipt of >1 line of pre-AHCT chemotherapy and year of AHCT 2008–2011 (compared to 2012–2014) were associated with worse OS in this cohort. HCT-CI and lines of treatment have been shown to be associated with OS in MM in multiple studies. (21–23) Similarly, receipt of more than 1 line of therapy prior to AHCT has not shown to be of benefit even among patients who achieve suboptimal response to first line of treatment. (24) Year of transplant is a close surrogate for use of maintenance therapy during this period. (24)(25) Indeed, in our study, 29% of patients were reported to receive maintenance in 2008–2011 compared to 51% in 2012–2014.

Survival following early relapse is poor despite availability of novel agents. The median overall survival of R-ISS I, II and III are 4.1, 2.5 and 1.5 years, respectively, in our analysis. R-ISS III at diagnosis was an independent prognostic factor even at the time of early relapse. Kumar et al. reported that in myeloma patients treated between 1994 and 2006, relapse within a year after AHCT confers poor prognosis, with median OS of 10.8 months from the time of relapse. (6) In our recent CIBMTR analysis, the median post relapse survival following early relapse was 24 months for those transplanted after 2005 compared with 16 months prior to 2005. (13) While there was improvement of post-relapse survival after 2005, the improvement has been minimal in the recent years and is similar to what we have observed in the current analysis. The marginal improvement in survival in this setting is likely due to access to new drugs such as pomalidomide, carfilzomib, daratumumab, elotuzumab and other clinical trials. We are able to show the robustness of R-ISS in predicting post-relapse survival with R-ISS III patients showing a far inferior OS of 1.5 years compared to R-ISS I patients showing 4.5 years post-relapse survival.

In our cohort of patients with an early post-AHCT relapse, two groups were identified, those who had received maintenance post-AHCT (N=127) or not (N=70). It is important to note that this analysis did not compare the rate of early relapse in maintenance versus non-maintenance groups. However, the receipt of maintenance did not affect survival in the early relapse group or the median duration to relapse after AHCT. This speaks to the fact that disease biology driving early relapse is probably the most important prognostic factor and newer strategies need to be devised for patients at risk of experiencing early relapse.

The year of transplant was not of prognostic significance in the early relapse group although it was significant for OS in the entire cohort. A significant majority of patients in the era spanning 2012–2014 received maintenance and may reflect the improved survival from maintenance strategies. However, this improvement in survival did not accrue to the early relapse group and again reflects the aggressive biology of disease that led to early relapse. HCT-CI and lines of pre-AHCT treatment remained significant predictors of post-relapse survival even among early relapses. Lastly, we observed that early relapse patients who had received full dose melphalan conditioning (200 mg/m2) had inferior post-relapse survival compared with early relapse following lower dose melphalan (140 mg/m2). Notably melphalan dose was not correlated with OS in the entire cohort. This intriguing finding suggests that early relapse of MM despite full conditioning intensity may behave more aggressively. This analysis is unable to determine the mechanism of this phenomenon: i.e. if early relapse after full melphalan dosage indicates relative refractoriness to subsequent therapies or clonal evolution with the addition of high risk markers induced by high dose melphalan in the setting of genomic instability or if there are other mechanisms mediating this observation.

A recent study by Kastritis et.al reported prognosis of unselected patients who were treated with novel agents using R-ISS staging. The conclusion was verified that R-ISS is a robust tool for risk stratification of newly diagnosed patients with symptomatic myeloma. (26)

Our analysis is limited by the relatively small sample size for the early relapse cohort. This may be reflective of the years of transplant that we studied when the R-ISS was not in full

clinical use. The R-ISS was developed in 2015, while our dataset extending between 2008–2014 captures the real-world practice of MM patients receiving AHCT, and we remain optimistic that LDH and FISH studies will be more universally adopted.

In summary, we report that R-ISS at diagnosis predicts the risk of early relapse post-AHCT. Further, the outcomes of patients with R-ISS III disease continue to be poor even in the era of novel drugs in the setting of early relapse and maintenance. Lastly, early relapse a dynamic marker for high risk disease, remains a therapeutic challenge and future studies should also address the prevention of early relapse. Myeloma therapy continues to advance with newer modes of targeted therapies such as monoclonal antibodies, bispecific antibodies, chimeric antigen receptor T-cells, and dendritic cell-based cancer vaccines. (27) Clinical trials targeting patients at risk for early relapse using such newer agents and novel combinations are necessary in order to effect a meaningful improvement in high risk disease.

References

1. Sonneveld P, Goldschmidt H, Rosiñol L, Bladé J, Lahuerta JJ, Cavo M, et al. Bortezomib-Based Versus Nonbortezomib-Based Induction Treatment Before Autologous Stem-Cell Transplantation in Patients With Previously Untreated Multiple Myeloma: A Meta-Analysis of Phase III Randomized, Controlled Trials. JCO. American Society of Clinical Oncology; 2013 9 10;31(26):3279–87.
2. Harousseau J-L, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005–01 Phase III Trial. JCO. 2010 10 20;28(30):4621–9.
3. Chng WJ, Dispenzieri A, Chim C-S, Fonseca R, Goldschmidt H, Lentzsch S, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. Nature Publishing Group; 2014 2 1;28(2):269–77.
4. Lahuerta JJ, Paiva B, Vidriales M-B, Cordón L, Cedena M-T, Puig N, et al. Depth of Response in Multiple Myeloma: A Pooled Analysis of Three PETHEMA/GEM Clinical Trials. JCO. American Society of Clinical Oncology; 2017 9;35(25):2900–10.
5. Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. Leukemia. Nature Publishing Group; 2013 8 9;28(2):258–68.
6. Kumar S, Mahmood ST, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone Marrow Transplant. Nature Publishing Group; 2008 6 30;42(6):413–20.
7. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Early relapse after single auto-SCT for multiple myeloma is a major predictor of survival in the era of novel agents. Bone Marrow Transplant. 2014 10 27;50(2):204–8. [PubMed: 25347006]
8. Hoering A, Crowley J, Shaughnessy JD, Hollmig K, Alsayed Y, Szymonifka J, et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in Total Therapy protocols. Blood. American Society of Hematology; 2009 8 13;114(7):1299–305.
9. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosiñol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. JCO. American Society of Clinical Oncology; 2016 9 22.
10. Scott EC, Hari P, Kumar S, Fraser R, Davila O, Shah N, et al. Staging Systems for Newly Diagnosed Myeloma Patients Undergoing Autologous Hematopoietic Cell Transplantation: The Revised International Staging System Shows the Most Differentiation between Groups. Biology of Blood and Marrow Transplantation. 2018 Aug.
11. International uniform response criteria for multiple myeloma. Leukemia. Nature Publishing Group; 2006 7 20;20(9):1467–73.

12. Scott EC, Hari P, Sharma M, Le-Rademacher J, Huang J, Vogl D, et al. Post-Transplant Outcomes in High-Risk Compared with Non–High-Risk Multiple Myeloma: A CIBMTR Analysis. Biology of Blood and Marrow Transplantation. Elsevier; 2016 10 1;22(10):1893–9.
13. Kumar SK, Dispenzieri A, Fraser R, Mingwei F, Akpek G, Cornell R, et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. Leukemia. Nature Publishing Group; 2018 1 5;:1–10.
14. Bergsagel PL, Mateos MV, Gutierrez NC, Rajkumar SV, San Miguel JF. Improving overall survival and overcoming adverse prognosis in the treatment of cytogenetically high-risk multiple myeloma. Blood. American Society of Hematology; 2013 2 7;121(6):884–92.
15. Haessler J, Shaughnessy JD, Zhan F, Crowley J, Epstein J, van Rhee F, et al. Benefit of Complete Response in Multiple Myeloma Limited to High-Risk Subgroup Identified by Gene Expression Profiling. Clinical Cancer Research. 2007 12 1;13(23):7073–9. [PubMed: 18056185]
16. Kazmi SM, Nusrat M, Gunaydin H, Cornelison AM, Shah N, Kebriaei P, et al. Outcomes Among High-Risk and Standard-Risk Multiple Myeloma Patients Treated With High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation. Clinical Lymphoma Myeloma and Leukemia. 2015 11;15(11):687–93.
17. Jakubowiak AJ, Chari A, Lonial S, Weiss BM, Comenzo RL, Wu K, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): An open-label, phase 1b study. JCO. American Society of Clinical Oncology; 2017 5 30.
18. A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma - Full Text View - ClinicalTrials.gov.
19. A Phase III Trial on the Effect of Elotuzumab in VRD Induction /Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma - Full Text View - ClinicalTrials.gov.
20. Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma - Full Text View - ClinicalTrials.gov.
21. Berro M, Arbelbide JA, Rivas MM, Basquiera AL, Ferini G, Vitriu A, et al. Hematopoietic Cell Transplantation–Specific Comorbidity Index Predicts Morbidity and Mortality in Autologous Stem Cell Transplantation. Biology of Blood and Marrow Transplantation. 2017 10;23(10):1646–50. [PubMed: 28669923]
22. Nadiminti K, Farooq U, Dozeman L, Mott S, Tricot GJ, Jethava Y, et al. Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) Score Predicts Non-Relapse Mortality (NRM) and Overall Survival (OS) in Multiple Myeloma Patients Undergoing Intensive Preparative Regimen with Autologous Stem Cell Transplantation (ASCT) Followed By Maintenance Therapy Using Novel Agents. Blood. 2017 12 7;130(Suppl 1):3281.
23. Saad A, Mahindra A, Zhang M-J, Zhong X, Costa LJ, Dispenzieri A, et al. Hematopoietic Cell Transplant Comorbidity Index Is Predictive of Survival after Autologous Hematopoietic Cell Transplantation in Multiple Myeloma. Biology of Blood and Marrow Transplantation. 2014 3;20(3):402–408.e1. [PubMed: 24342394]
24. Vij R, Kumar S, Zhang M-J, Zhong X, Huang J, Dispenzieri A, et al. Impact of Pretransplant Therapy and Depth of Disease Response before Autologous Transplantation for Multiple Myeloma. Biology of Blood and Marrow Transplantation. Elsevier Inc; 2015 2 1;21(2):335–41.
25. D'Souza A, Zhang M-J, Huang J, Fei M, Pasquini M, Hamadani M, et al. Trends in pre- and post-transplant therapies with first autologous hematopoietic cell transplantation among patients with multiple myeloma in the United States, 2004–2014. Leukemia. 2017 6 30;31(9):1998–2000. [PubMed: 28663578]
26. Kastritis E, Terpos E, Roussou M, Gavriatopoulou M, Migkou M, Eleutherakis-Papaiakovou E, et al. Evaluation of the Revised International Staging System in an independent cohort of unselected patients with multiple myeloma. Haematologica. Haematologica; 2017 2 28;102(3):593–9. [PubMed: 27789676]
27. Podar K, Jäger D. Targeting the immune niche within the bone marrow microenvironment: The rise of immunotherapy in Multiple Myeloma. Current Cancer Drug Targets. 2017 2 14;17(999):1–1.

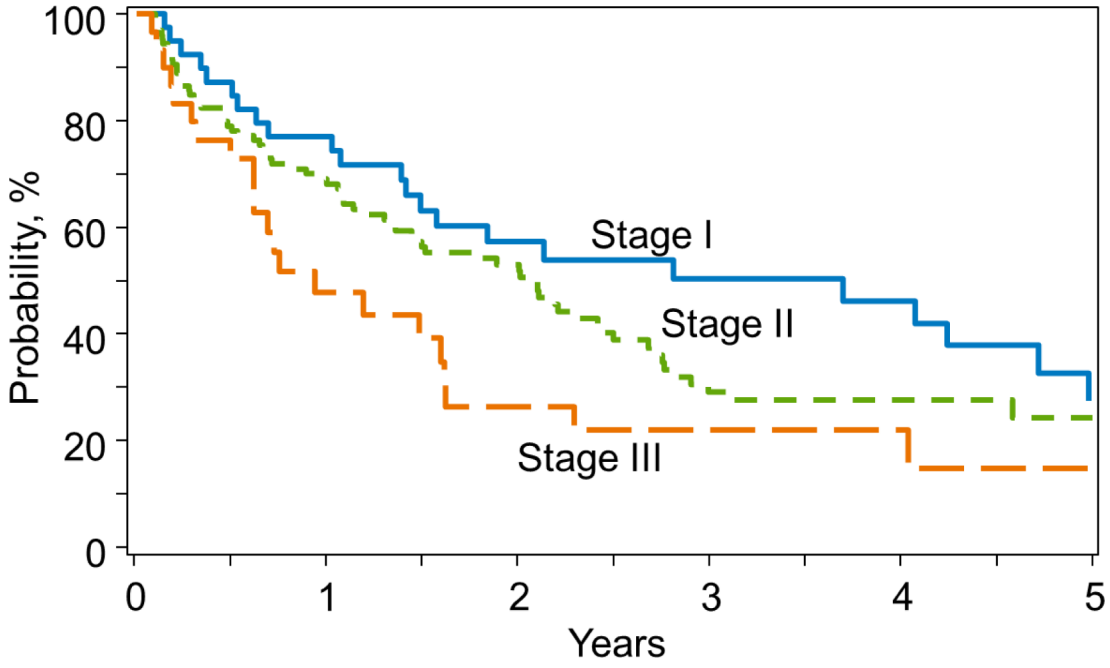

Figure 1.
Post-relapse survival of early relapsers by R-ISS

Table 1.

Characteristics of US adult patients who underwent melphalan base first auto PB MM transplant from 2008–2014 and reported with CIBMTR

	R-ISS I	R-ISS II	R-ISS III
Number of patients	**199**	**360**	**69**
Number of centers	55	64	33
Median age at HCT (range)	59 (41–76)	60 (40–78)	60 (43–75)
Male Gender	115 (58)	213 (59)	41 (59)
Karnofsky score			
90–100	120 (60)	198 (55)	35 (51)
<90	73 (37)	156 (43)	29 (42)
Missing	6 (3)	6 (2)	5 (7)
HCT-CI			
0	85 (43)	108 (30)	15 (22)
1	28 (14)	61 (17)	9 (13)
2	26 (13)	66 (18)	15 (22)
≥3	60 (30)	122 (33)	30 (43)
Missing	0	3 (<1)	0
Clinical Trial Enrollment	76 (38)	118 (33)	18 (26)
LDH at diagnosis ≥ upper limit	0	71 (20)	58 (84)
ISS stage at diagnosis			
Stage I	199	45 (13)	0
Stage II	0	214 (59)	0
Stage III	0	101 (28)	69
Cytogenetic abnormality (conventional or FISH)			
t(4;14)only	0	16 (4)	8 (12)
t(14; 16) only	0	4 (1)	3 (4)
Del17p only	0	14 (4)	4 (6)
1q abnormality	13 (7)	25 (7)	5 (7)
≥ 2 High risk	0	9 (3)	5 (7)
No high risk Abnormality	186 (93)	292 (81)	44 (64)
Lines of chemotherapy			
1	170 (85)	289 (80)	49 (71)
≥2	29 (15)	71 (20)	20 (29)
Pre-transplant induction chemotherapy *			
VTD	15 (8)	18 (5)	5(7)
VRD	89 (45)	162 (45)	31 (45)
VCD	29 (15)	59 (16)	15 (22)
VD	17 (9)	37 (10)	9 (13)
RD	35 (18)	68 (19)	5 (7)
TD	14 (7)	16 (4)	4 (6)
Disease status prior to HCT **			

	R-ISS I	R-ISS II	R-ISS III
sCR/CR	41 (21)	70 (19)	12 (17)
VGPR	55 (28)	122 (34)	24 (35)
PR/SD/PD	103 (52)	168 (47)	11 (48)
Melphalan dose (mg/m^2)			
140	46 (23)	89 (25)	19 (28)
200	153 (77)	271 (75)	50 (72)
Time from diagnosis to transplant			
≤ 6 months	69 (35)	139 (39)	31 (45)
6–12 months	110 (55)	172 (48)	29 (42)
12–18 months	20 (10)	49 (14)	9 (13)
Year of transplant			
2008	44 (22)	94 (26)	11 (16)
2009	17 (9)	32 (9)	6 (9)
2010	8 (4)	23 (6)	10 (14)
2011	30 (15)	46 (13)	6 (9)
2012	39 (20)	46 (13)	8 (12)
2013	30 (15)	70 (19)	9 (13)
2014	31 (16)	49 (14)	19 (28)
Planned post-transplant treatment	147 (74)	245 (68)	48 (70)
Median follow-up of survivors (range), months	47 (6–97)	48 (3–99)	40 (12–97)

*Abbreviation: Bortezomib (V), Thalidomide (T), Dexamethasone (D), Lenalidomide (R), Cyclophosphamide (C)

**Abbreviation: Stringent complete response (sCR), Complete response (CR), Very good partial response (VGPR), Partial response (PR), Stable disease (SD), Progressive disease (PD)

Table 2.

Univariate analysis (R-ISS stage)

	Stage I (N = 199)		Stage II (N = 360)		Stage III (N = 69)		
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**p-value**
Relapse/progression	198		358		69		<0.001
1-year		10 (6–14)%		21 (17–26)%		38 (27–49)%	<0.001
2-year		23 (17–29)%		39 (33–44)%		50 (38–62)%	<0.001
3-year		35 (28–42)%		50 (44–55)%		65 (51–78)%	<0.001
PFS	198		358		69		<0.001
1-year		90 (85–94)%		77 (72–81)%		61 (49–72)%	<0.001
2-year		77 (70–82)%		59 (54–64)%		47 (35–59)%	<0.001
3-year		64 (57–71)%		47 (41–53)%		32 (20–45)%	<0.001
Overall survival	199		360		69		<0.001
1-year		97 (95–99)%		93 (90–95)%		88 (80–95)%	0.005
2-year		96 (92–98)%		85 (81–88)%		71 (59–82)%	<0.001
3-year		88 (83–93)%		75 (70–80)%		56 (43–69)%	<0.001

* Abbreviation: N, number; Prob, probability; Eval, evaluable; CI, confidence interval; PFS, progression-free survival

Table 3.

Multivariate analysis for OS for the whole cohort (R-ISS)

Parameter	Level	N		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
		606					
R-ISS			Overall				0.0004
	I	193		1.00			
	II	349		1.83	1.225	2.726	0.003
	III	64		2.82	1.657	4.813	0.0001
HCT Comorbidity Index			Overall				0.013
	0	204		1.00			
	1–2	199		1.02	0.687	1.526	0.907
	3+	203		1.66	1.129	2.444	0.010
Lines of Chemotherapy			Overall				0.007
	1	491		1.00			
	2+	115		1.65	1.14	2.30	0.007
Year of Transplant			Overall				0.006
	2012–2014	296		1.00			
	2008–2011	310		1.77	1.179	2.652	0.006

*Abbreviation: OS, overall survival; R-ISS, Revised-International Staging System; N, number; HCT, hematopoietic cell transplantation

Table 4.

Multivariate Analysis of OS in patients who relapse early (Analysis limited patients relapsing <24 mo post transplant)

Parameter	Level	N		Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
		197					
R-ISS			Overall				0.036
	I	42		1.00			
	II	126		1.31	0.824	2.089	0.252
	III	29		2.15	1.190	3.879	0.011
HCT-CI			Overall				0.017
	0	65		1.000			
	1–2	61		0.95	0.593	1.520	0.827
	3+	71		1.69	1.091	2.624	0.019
Lines of Chemotherapy			Overall				0.037
	1	146		1.00			
	2+	51		1.52	1.026	2.252	0.037
Melphalan Dose			Overall				0.023
	140	54		1.00			
	200	143		1.65	1.072	2.537	0.023

*Abbreviation: N, number; R-ISS, Revised-International Staging System; HCT-CI, hematopoietic cell transplantation-comorbidity index

Table 5.

Univariate analysis of impact of maintenance in the early relapse group (Post relapse overall survival in maintenance vs no maintenance)

	No planned post-maintenance		Planned post-maintenance		
Number of patients		**127**		**70**	
Best response post-transplant					
≥VGPR		59 (46)		39 (56)	
<VGPR		68 (54)		31 (44)	
Median time to relapse after transplant		10 (<l-24)		12 (1–24)	
Overall survival post relapse					
	N Eval	Prob (95% CI)	N Eval	Prob (95% CI)	P-value
	127		70		0.86
1-year		67 (59–76)%		66 (54–77)%	0.82
2-year		48 (39–57)%		51 (39–64)%	0.67
3-year		30 (21–39)%		38 (24–53)%	0.33

*Abbreviation: N, number; Eval, evaluable; Prob, probability; CI, confidence interval