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Bone Marrow Transplant. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Bone Marrow Transplant. 2015 August ; 50(8): 1075–1082. doi:10.1038/bmt.2015.106.

High dose therapy and autologous stem cell transplant in older adults with multiple myeloma

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Abstract

Randomized trials showing that high dose therapy with autologous stem cell transplant (ASCT) improved overall survival in multiple myeloma (MM) excluded patients over age 65. To compare outcomes of older adults with MM who underwent ASCT with non-transplant strategies, we identified 146 patients age 65 – 77 with newly diagnosed MM seen Washington University School of Medicine from 2000–2010. Survival among patients who did (N=62) versus did not (N=84) undergo ASCT was compared using Cox proportional hazards modeling, controlling for comorbidities, ECOG performance status (PS) and propensity to undergo ASCT. Median age was 68 (range 65–77). PS and comorbidities did not differ significantly between those who did *vs*. did not undergo ASCT. Median overall survival was significantly longer in patients who underwent ASCT than those who did not [median 56.0 months (95% confidence intervals 49.1–65.4) *vs.* 33.1 months (24.3–43.1), p=0.004]. Adjusting for PS, comorbidities, Durie-Salmon stage and propensity to undergo ASCT, ASCT was associated with superior overall survival [HR for mortality 0.52 (95% CI 0.30–0.91), p=0.02]. In a cohort of older adults with MM, undergoing ASCT was associated with a nearly 50% lower mortality, after controlling for PS, comorbidities, stage and propensity to undergo ASCT.

Introduction

Multiple myeloma (MM) is a disease of older adults, with almost two-thirds of cases occurring in patients over the age of 65 years. With the aging of the population, the number

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Conflict of Interest

The authors have no relevant conflicts of interest.

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of older adults with MM is expected to nearly double by the year 2030.(1) While advances in treatment have improved survival rates substantially, the improvement among older adults have been modest compared to that among younger adults.(2,3) Advancing age is one of the most important negative prognostic factors in MM.(4) The factors underlying this age-related disparity in prognosis are likely related to a combination of factors, including comorbidity, performance status, decreased physiologic reserve, social support, referral bias and undertreatment.(5)

In randomized trials, high dose therapy with autologous stem cell transplantation (ASCT) prolongs survival in patients with MM, compared to conventional chemotherapy.(6,7) However, these studies specifically excluded patients over the age of 65, with a median age of enrolled patients of 55–57 years. Retrospective studies suggest that select older adults can tolerate ASCT and benefit to the same extent that younger individuals do(8–11), but the role of ASCT in older adults in the era of modern therapy with immunomodulatory agents and proteasome inhibitors is unclear.

Thus, we sought to examine relationships between baseline factors and initial MM treatment strategy with or without ASCT and to then compare survival between older adults who did *versus* did not undergo ASCT as part of their initial treatment.

Subjects and methods

Patients

With the approval of the Human Studies Committee, we identified all patients age 65 years and older with multiple myeloma diagnosed or treated at Washington University School of Medicine 2000–2010 from the Barnes-Jewish Hospital Oncology Data Services cancer registry. Patients with amyloid, smoldering MM or other concomitant malignancies were excluded. Patients who received no treatment/palliative care or corticosteroids only were excluded. Because in the United States, the Center for Medicare and Medicaid Services policy excluded coverage of ASCT for individuals over age 77 through 2003, we restricted the analyses to patients aged 77 years and younger. To mitigate immortal time bias, patients who survived fewer than 4 months and thus would not have survived to proceed to ASCT were excluded.

Clinical Data

The Barnes-Jewish Hospital Oncology Data Services cancer registry includes data on the age, gender, race, insurance status, and comorbidities. Comorbidities were graded using the ACE-27 Index.(12) Insurance status/payer was categorized as Medicare alone or with a supplemental plan, Medicare managed care plan, Medicare/Medicaid dual-eligible, and Other/Unknown. Medical records were reviewed for data not available within the Oncology Data Services Registry, including ECOG performance status(13), body mass index (BMI), baseline laboratory values, staging, details on pathology, cytogenetics, paraprotein isotype, and initial treatment, including whether the patient underwent high-dose therapy and autologous stem cell transplant as part of initial therapy. Creatinine clearance was calculated using the Cockcroft-Gault equation.(14) Staging was determined using both the Durie-

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Salmon Staging System(15) and the International Staging System (ISS).(16) Initial treatment was categorized as: conventional agents (such as melphalan or doxorubicin-based regimens) with corticosteroids, novel agents (thalidomide, lenalidomide or bortezomib) with corticosteroids, novel agents with a second agent and corticosteroids. As common in retrospective studies, missing data presented a potential challenge to this study though every effort has been made to retrieve patient and clinical data. Among the 10 clinicopathologic factors considered, 5 covariates (ASCT status, age, gender, race and insurance status) had complete data, while the other 5 covariates had some extent of missing values - ACE-27 comorbidity index (n=7, 5%), initial therapy (n=35, 24%), Durie-Salmon stage (n=41, 28%), ECOG performance status (n=42, 29%), and creatinine clearance (n=49, 34%). Rather than omit patients with missing values, multivariate regression models were used to impute the missing values.(17) Specifically, the 5 covariates with complete data were first used to impute the comorbidity index, which had only a few missing values, and then these covariates were used as predictors for the remaining covariates with more missing data. To better satisfy the assumption of "missing at random", we also included body mass index (BMI) and several other baseline laboratories (WBC, HGB, ANC, and platelets) in the regression models for multiple imputations.

Statistical Analyses

The primary endpoint was overall survival (OS) defined as time from diagnosis until death, censored at last follow-up. The distribution of demographic and clinical characteristics between patients with and without ASCT was compared using Fisher's exact test, Mann-Whitney rank-sum test, or two-sample t-test as appropriate. For significantly imbalanced factors, multivariate logistic regression was used to create propensity scores for undergoing ASCT.(18) Survival curves by ASCT status were estimated using the Kaplan-Meier product-limit method and compared by log-rank test. Univariate Cox proportional hazard models were fitted to identify factors significantly related to OS. To assess whether ASCT was an independent predictor of OS, a multivariate Cox model was constructed to adjust for other significant predictors as well as propensity scores. Multivariate regression models were used to impute the missing values in the predictors.(17) All analyses were two-sided and significance was set at a p-value of 0.05. Statistical analyses were performed using SAS 9.2 (SAS Institutes, Cary, NC).

Results

A total of 199 patients were initially identified. Fifty-three patients who were over age 77, who received only supportive care or corticosteroids, or survived fewer than 4 months were excluded. This resulted in an analysis cohort of 146 patients; baseline characteristics are presented in Table 1.

Regarding staging and baseline prognostic factors, beta-2-microglobulin was not available for the majority of patients in the cohort; therefore, ISS stage was not included in the analyses. Cytogenetics were not performed for most of the patients in the cohort, and therefore this variable was excluded from analysis. Of those for whom data on cytogenetics and/ or fluorescence in situ hybridization for common chromosomal abnormalities were

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performed, 13.3% (4 of 30 tested) had translocation t(4;14), 32.5% (13 of 40 tested) had deletion 13, 9.7% (3 of 31 tested) had translocation t(11;14), 11.8% (4 of 34 tested) had deletion 17p, 10.5% (6 of 57 tested) had hypodiploidy and 21.2% (12 of 57 tested) had hyperdiploidy.

Induction regimens are listed in Table 1. Over half (57.5%, N=84) of the cohort did not undergo ASCT, while 42.5% (N=62) did. Of those who underwent ASCT, all but one received melphalan 200 mg/m^2 for conditioning; one received melphalan 140 mg/m^2. No patients underwent tandem ASCT. One patient who underwent ASCT died within 100 days due to toxicity, yielding a 100-day non-relapse mortality rate of 1.6%. Following ASCT, most (85.5%) did not receive maintenance therapy; 2 patients (3.2%) received thalidomide maintenance, 3 (4.8%) received bortezomib maintenance and 4 (6.4%) received lenalidomide maintenance. Data on response to initial therapy was available in only 44% (37/84) of patients who did not undergo ASCT; in the 37 in whom response was assessable, 78.4% achieved PR or better. In those who underwent ASCT, most (88.7%, 55/62) had data available allowing ascertainment of response, with 98% achieving PR or better. Chi-square analysis was not performed due to concern for ascertainment bias, given the significant imbalance in proportion of patients with data available for ascertainment of response in the two treatment groups.

The median overall survival of the entire cohort was 43.4 months [95% Confidence Intervals (CI) 39.8 – 52.9 months]. The median follow-up time for censored patients was 48.4 months (range 5.5 – 141.7 months). As would be expected, there were imbalances in some baseline characteristics between patients who did *versus* did not undergo ASCT: Patients who did not undergo ASCT tended to be older and were more likely to be Medicare-Medicaid dual-eligible (Table 1). The median OS in the cohort that did not undergo ASCT was 33.1 months (95% CI 24.3–43.1) while the median OS in the cohort that did undergo ASCT was 56.0 months (95% CI 49.1–65.4)(Figure 1). The 3-year overall survival was 78.3% (95% CI 68.2–90.0%) among those who did undergo ASCT versus 49.5% (95% confidence intervals 39.8–61.5%) for those who did not.

On univariate analysis, ASCT and performance status were associated with overall survival (Table 2). Race, gender, comorbidities, insurance, creatinine clearance and initial therapy were not associated with survival. The multivariate analysis was summarized over 10 imputed datasets. After controlling for performance status, comorbidity, stage and propensity to undergo ASCT, ASCT remained associated with superior overall survival [Hazard Ratio (HR) for death 0.52 (95% CI 0.30–0.91), p=0.02]. To visualize the results, Figure 2 also presents the Kaplan-Meier curves for 48 pairs of patients, matched by the propensity scores to undergo ASCT, from the first imputed dataset.

To interrogate our findings, we performed sensitivity analyses. First, we compared survival by treatment in the subgroups aged 65–69 and those aged over 70 (Figure 3), with similar results. ASCT was associated with superior overall survival in both subgroups, though the HR failed to meet significance in the strata of patients over age 70 [Age 65–69 HR for death 0.60 (95% CI 0.36–1.00), p=0.049); Age ≥70 HR 0.33 (95% CI 0.10–1.07), p=0.066]. Second, further attempt to mitigate immortal time bias and confounding by

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indication(19,20), we performed a 12-month landmark analysis, excluding patients with follow-up less than 1 year (Figure 4). On a multivariate analysis including performance status, comorbidity and age≥70, ASCT was still associated with a significantly superior survival [HR for death 0.49 (95% CI 0.25–0.94), p=0.03]. Finally, in multivariate analysis in which ASCT was treated as a time-dependent variable, ASCT maintained its association with superior survival [HR for death 0.44 (95% CI 0.25–0.78), p=0.0048].

Discussion

In this study, we show that, among adults over age 65 with MM, undergoing ASCT is associated with a nearly 50% reduction in the hazard ratio for mortality, after controlling for potential confounders including performance status, comorbidity, stage and propensity to undergo ASCT. This finding supports the potential utility of ASCT among older adults with MM who are deemed eligible for this treatment option.

Our findings add to the current literature regarding the benefit of ASCT among older adults, some of which is conflicting. While the superiority of ASCT over conventional therapy in younger adults with MM was established by randomized trials,(6,7) its utility among older adults is less well-established. A number of studies have compared outcomes of ASCT in older adults with MM to outcomes in younger patients and demonstrated similar response rates, progression-free survival and overall survival.(9,21–23) This line of evidence presupposes that if ASCT is superior to conventional therapy in younger adults, and the outcomes of ASCT are similar in younger and older patients, then ASCT is superior in older patients as well. However, other studies have suggested lower complete response rates and lower overall survival among older adults (Table 3).(11,24,25)

Studies directly comparing outcomes among older adults who did undergo ASCT with older adults who did not are few, and similarly inconsistent (Table 4). In a randomized trial of melphalan and prednisone (MP) versus melphalan, prednisone and thalidomide (MPT) versus induction chemotherapy followed by intermediate-dose melphalan (MEL100) and ASCT, MPT produced similar complete response rates and superior overall survival compared to ASCT following MEL100.(26) However, this dose of melphalan is inferior to higher doses of melphalan(27), and does not refute the potential role of higher dose melphalan ASCT in older adults. In a population-based registry by the Nordic Myeloma Study Group, older adults (aged 60–64 in their cohort) who underwent ASCT had lower mortality than patients who did not, with a reduction in risk similar to that in our present study [Risk ratio 0.65 (95% confidence intervals 0.42–0.92), p=0.02].(25) In a recent cohort patients with MM diagnosed between 2001 and 2010, patients over age 65 who received ASCT experienced longer median overall survival compared to older patients who did not undergo ASCT [median OS not reached (95% confidence intervals 5.4 years – not reached) with ASCT compared with 3.1 years (95% CI 2.5, 3.7) for those who did not, P<0.01].(3) Finally, in a retrospective cohort study of 318 patients aged 65–70, including 38 who underwent ASCT, ASCT was associated with improved OS on univariate analysis but not on multivariate analysis.(28) Thus, further study is needed to clarify the role of ASCT in older adults in the era of modern therapy.

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There are a number of limitations to our study. First, as an observational study, there are a number of potential confounders. Patients were selected for ASCT by clinicians who incorporate multiple facets of an older adult's health into the decision, such as laboratory values, comorbidities, performance status and patient preference. We attempted to control for differences in the populations who did versus did not undergo ASCT by controlling for performance status, comorbidity, stage and propensity to undergo ASCT in the multivariate model of survival and still saw a benefit associated with ASCT. Further, we saw persistence of the improvement in OS in a 12-month landmark analysis and treating ASCT as a time-dependent variable. It is possible that the survival benefit seen among the patients who underwent ASCT is related to residual confounding by additional factors which are *associated* with treatment allocation and directly impact prognosis, but unmeasured in our study: for example, functional status, as measured by scales such as the Katz Activities of Daily Living(29) or the Lawton Instrumental Activities of Daily Living (IADL) Scale(30). Dependence in IADLs is predictive of chemotherapy toxicity(31,32); since toxicity of therapy is associated with poorer survival in older adults with myeloma,(33) imbalances in geriatric assessment parameters such as functional status between the groups may explain the differences in survival seen in our study, rather than ASCT. Future studies that comprehensively evaluate the health of older adults with MM, including common geriatric syndromes such as functional dependence, impaired cognition and social support, are needed to ensure analyses to control for differences in the populations who undergo different treatment strategies.

In our analysis cohort, which was restricted to older adults who survived 4 months after diagnosis (and thus would have potentially been eligible for ASCT) and those under age 78, comorbidities were not independently associated with survival. Kleber *et al* developed a comorbidity index which is prognostic in MM, independent of International Staging System (ISS) stage.(34,35) The comorbidity index developed by Kleber *et al* includes the Karnofsky performance status (KPS) ≤70% as an independent prognostic factor; ECOG performance status was associated with survival in our model on univariate, but not multivatiate analysis. In our model, we employed the ACE-27 comorbidity index, which does not include performance status. The lack of prognostic power of comorbidities in this cohort may simply reflect the relatively small samples size, or that the discriminatory power of the ACE-27 comorbidity index is limited when the cohort is restricted to patients who survived 4 months after diagnosis (i.e. there were only 13 patients categorized as having severe comorbidities).

Another limitation of our study is the lack of disease-specific prognostic data, including ISS stage, cytogenetics and response to initial therapy. Given that we included cases from 2000–2010, prior to the promulgation of the ISS stage, many patients did not have data on beta-2-microglobulin to allow calculation of the ISS stage.(16) In addition, data on cytogenetics and fluorescence in *situ* hybridization for specific chromosomal abnormalities were frequently not available and could not be included in the survival model. It is possible that there were differences in the biology of disease that could explain the observed differences in survival, such that those with more aggressive biology of disease were less likely to undergo ASCT.

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In conclusion, in a cohort of patients with multiple myeloma over the age of 65, undergoing ASCT was associated with superior survival, with a nearly 50% lower risk of mortality after controlling for comorbidities, performance status, stage and propensity to undergo ASCT. We recognize the limitations of a retrospective cohort study in examining all of the factors associated with treatment selection, which may confound the association between treatment and outcomes. Future studies must focus on prospectively incorporating greater detail on disease characteristics, functional status and other geriatric assessment parameters in order to further perform comparative effectiveness research to clarify the role of ASCT in older adults with multiple myeloma.

Acknowledgements

This publication was made possible by Grant Numbers KM1CA156708 and K12CA167540 through the National Cancer Institute (NCI) at the National Institutes of Health (NIH) and Grant Number UL1 TR000448 through the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCI, NCATS or NIH. The authors also wish to acknowledge the support of the Biostatistics Core, Siteman Comprehensive Cancer Center and NCI Cancer Center Support Grant *P30 CA091842*.

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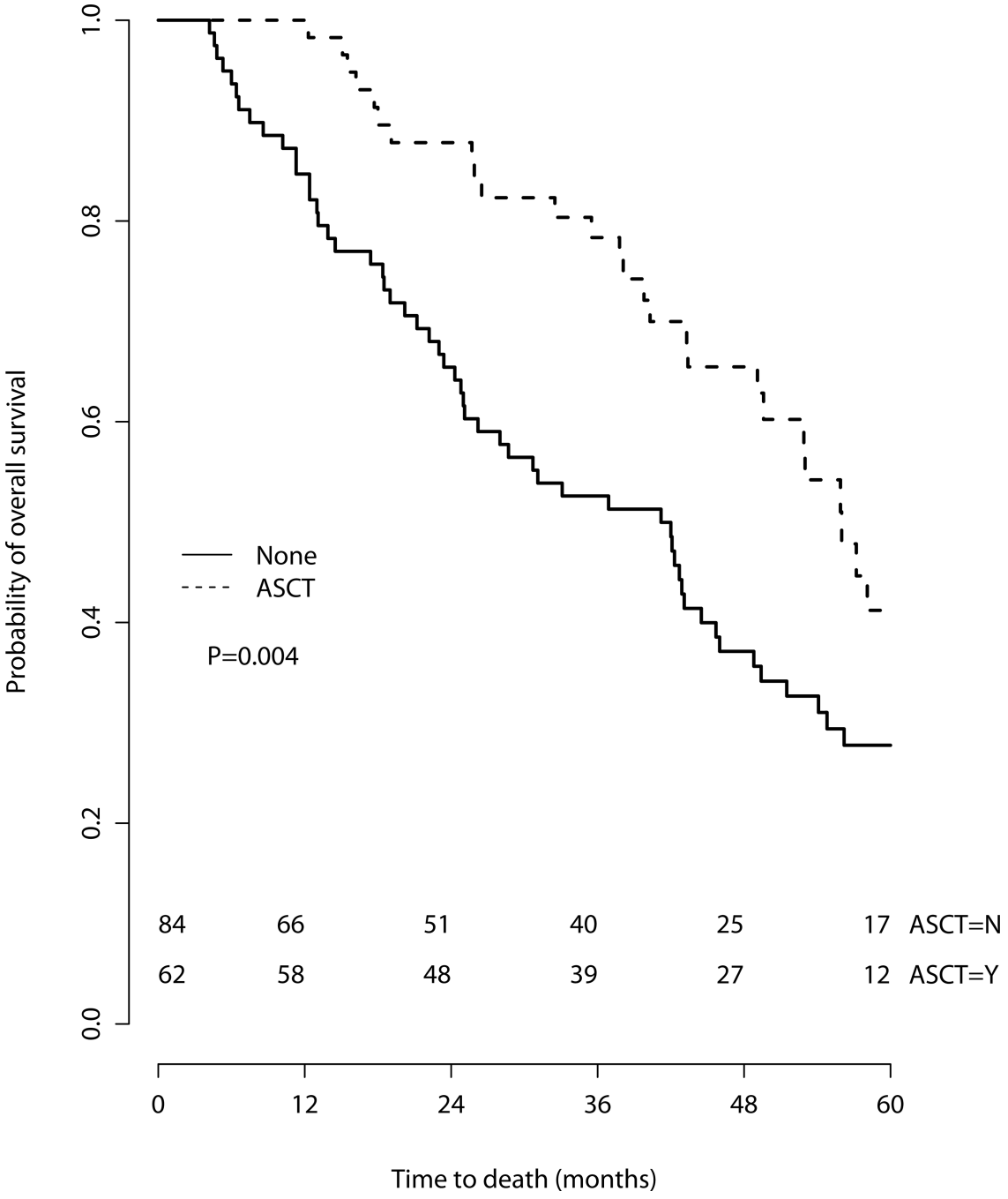

Figure 1.
Overall survival of entire cohort by treatment

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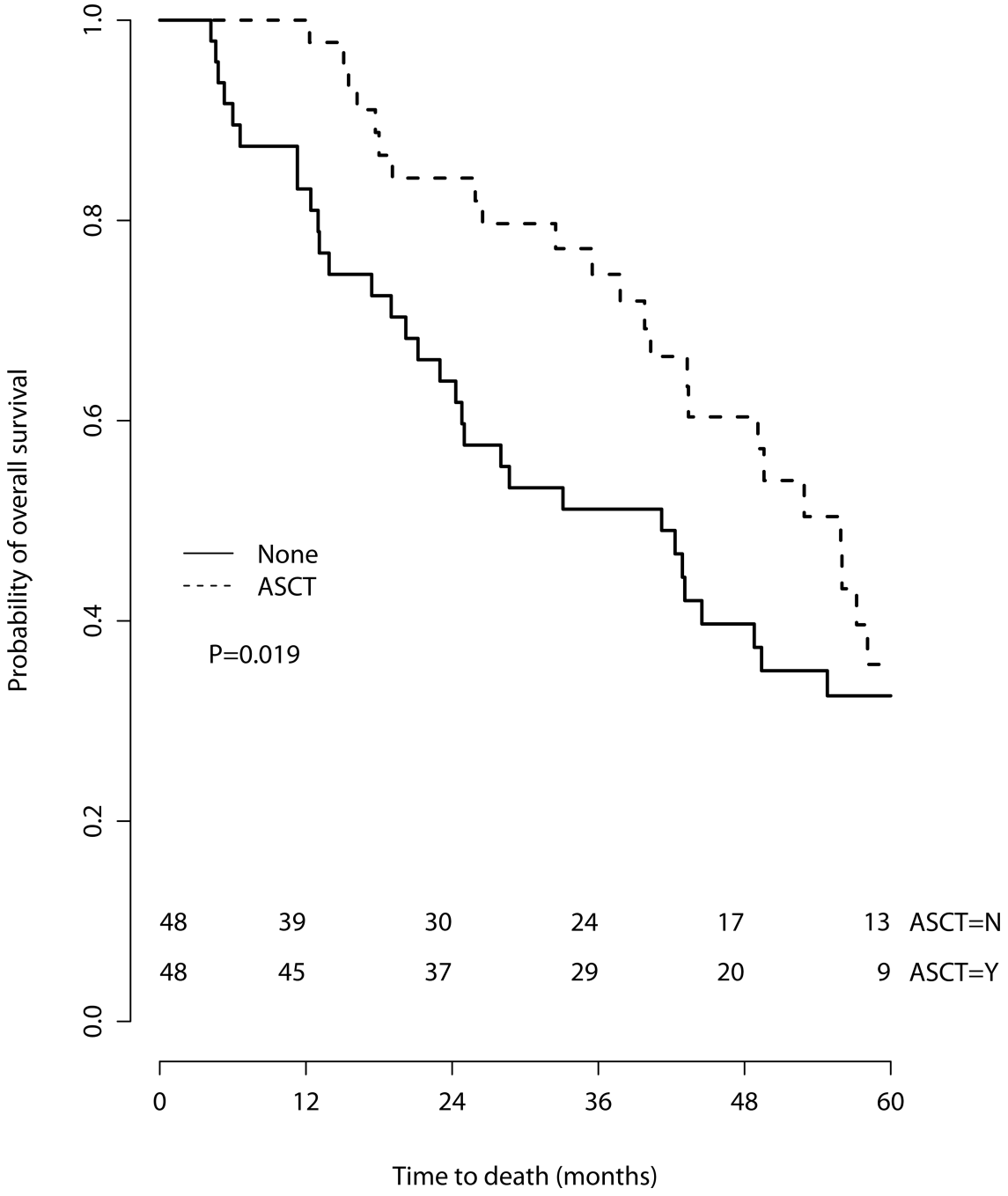

Figure 2.
Overall survival of 48 propensity-score matched pairs

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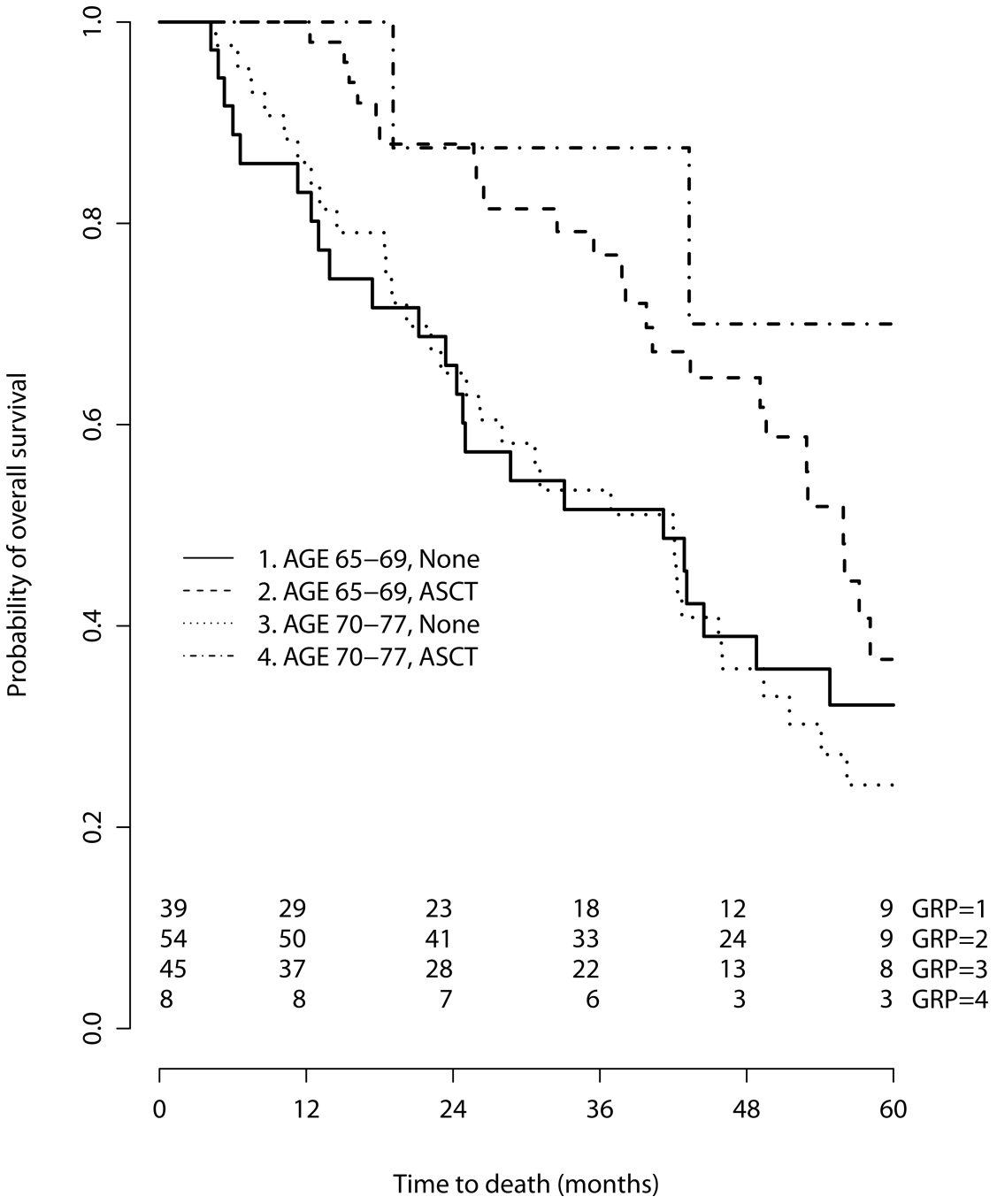

Figure 3.
Overall survival, stratified by age group

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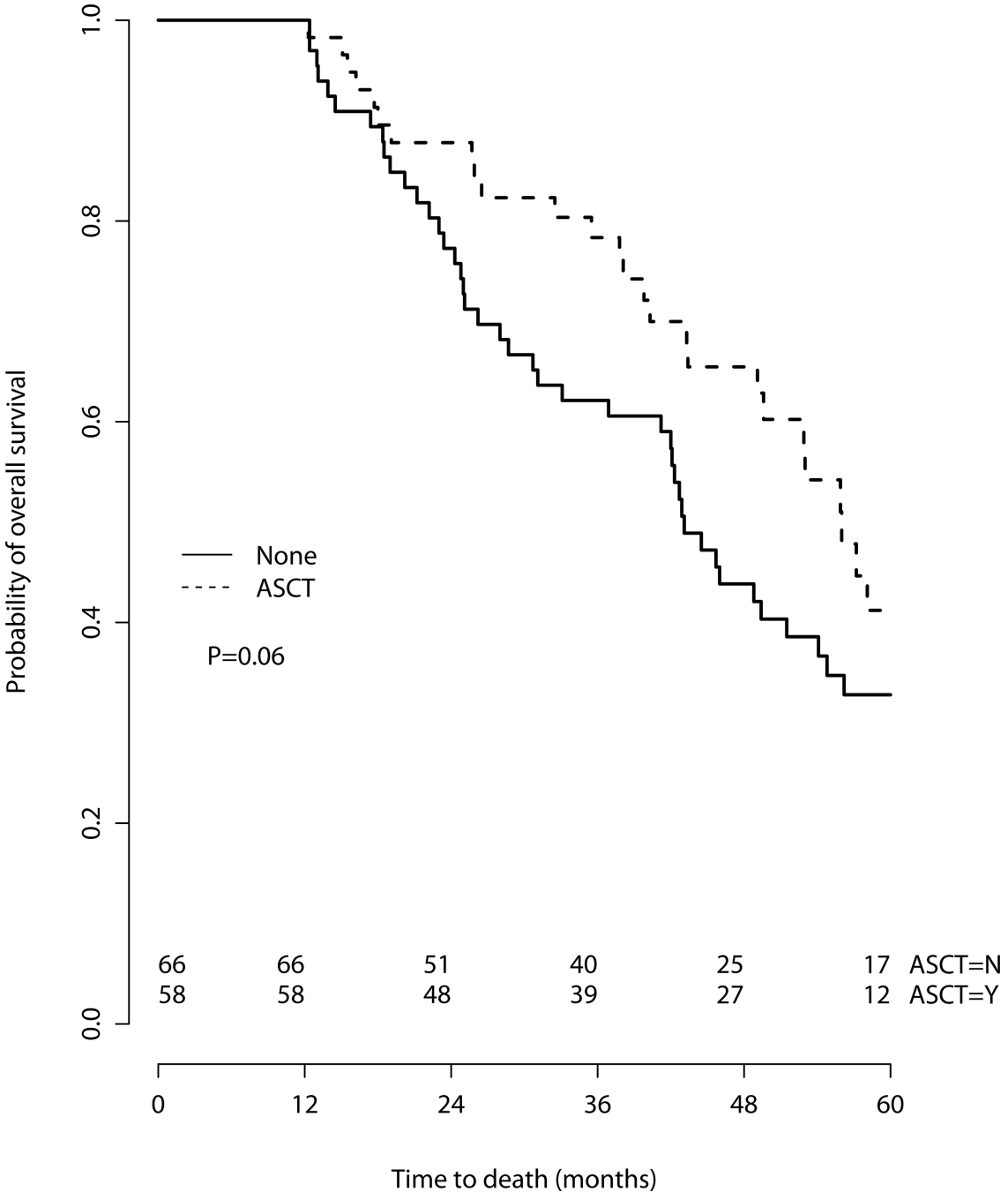

Figure 4.
12-month landmark analysis, overall survival

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Table 1

Baseline characteristics

	Entire cohort (n = 146)	Subgroups		
		Nontransplant (n = 84)	ASCT (n = 62)	P
Age (median, range)	68 (65 – 77)	70 (65 – 77)	67 (65 – 74)	<0.0001
Male Gender(frequency, percent)	77 (52.7%)	50 (59.5%)	27 (43.5%)	0.06
Race				0.2
White	119 (81.5%)	65 (77.4%)	54 (87.1%)	
Other	27 (18.5%)	19 (22.6%	8 (12.9%)	
Ace-27 comorbidity index (frequency*, percent)				0.12
None	35/139 (25.2%)	16/77 (20.8%)	19 (30.6%)	
Mild	61/139 (43.9%)	35/77 (45.4%)	26 (41.9%)	
Moderate	30/139 (21.6%)	15/77 (19.5%)	15 (24.2%)	
Severe	13/139 (9.4%)	11/77 (14.3%)	2 (3.2%)	
Durie-salmon stage (frequency*, percent)				0.14
1	10/105 (9.5%)	1/46 (2.2%)	9/59 (15.2%)	
2	19/105 (18.1%)	9/46 (19.6%)	10/59 (17.0%)	
3	76/105 (72.4%)	36/46 (78.3%)	40/59 (67.8%)	
ECOG performance status (frequency*, percent)				0.55
0	19/104 (18.3%)*	9/45 (20.0%)	10/59 (17.0%)	
1	53/104 (51.0%)	19/45 (42.2%)	34/59 (57.6%)	
2	22/104 (21.2%)	13/45 (28.9%)	9/59 (15.2%)	
3	10/104 (9.6%)	4/45 (8.9%)	6/109 (10.2%)	
Insurance				0.02
Medicare +/− supplement	120 (82.2%)	72 (85.7%)	48 (77.4%)	
Medicare managed care	14(9.6%)	5 (6.0%)	9 (14.5%)	
Medicare/Medicaid dual-eligible	5 (3.4%)	5 (6.0%)	0	
Other/unknown	7 (4.8%)	2 (2.4%)	5 (8.1%)	
Initial therapy				0.3
Novel combination therapy**	18 (16.2%)	7 (14.3%)	11 (17.7%)	
Novel agent	65 (58.6%)	26 (53.1%)	39 (62.9%)	
Alkylating agents	28 (25.2%)	16 (32.7%)	12 (19.4%)	
Creatinine clearance (Median, range)	60.9 ml/min (8.7–126.4)	58.0 ml/min (8.7–126.3)	64.1 ml/min (16.8 – 126.4)	0.2

*Denominator reflects missing data.

**Indicates an immunomodulatory agent or proteosome inhibitor with a second agent plus corticosteroids

ASCT, high dose therapy with autologous stem cell transplant

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Table 2

Factors associated with overall survival

	Univariate analysis		Multivariate analysis*	
	Hazard Ratio (95% confidence intervals)	P	Hazard Ratio (95% confidence intervals)	P
Transplant vs no transplant	0.54 (0.35–0.82)	0.004	0.52 (0.30–0.91)	0.02
Age	1.03 (0.97–1.09)	0.33		
Male gender	1.30 (0.87–1.96)	0.2		
Race (other relative to white)	1.40 (0.84–2.33)	0.2		
Performance status				
0	Ref	-	Ref	-
1	2.2 (1.04–4.92)	0.04	1.85 (0.74 – 4.63)	0.18
2	3.35 (1.41–7.95)	0.006	2.71(0.79 – 9.29)	0.11
3	3.54 (1.34–9.31)	0.01	2.79 (0.79 – 9.81)	0.11
Comorbidity				
None	Ref	-		
Mild	1.25 (0.73–2.12)	0.42	1.33 (0.72–2.44)	0.36
Moderate	1.24 (0.67–2.31)	0.5	1.31 (0.64–2.70)	0.46
Severe	1.73 (0.78–3.82)	0.17	1.99 (0.73–5.44)	0.18
Insurance				
Medicare +/− supplemental	Ref	-		
Medicare managed care	1.0 (0.50–1.99)	0.99		
Medicaid	1.74 (0.63–1.79)	0.28		
Other	0.66 (0.21–2.09)	0.48		
Creatinine clearance	1.0 (0.99–1.01)	0.44		
Initial therapy				
Novel combination therapy	Ref	-		
Novel agent + steroids	1.19 (0.58–2.48)	0.64		
Alkylating agents	1.21 (0.56–2.68)	0.62		
Durie salmon stage				
1	Ref	-	Ref	-
2	1.60 (0.50–5.14)	0.43	1.06 (0.31–3.59)	0.93
3	2.56 (0.93–7.16)	0.069	0.93 (0.30–2.86)	0.9

*Adjusted for other variables in the model and propensity to undergo transplant.

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Table 3

Study	Study design	Subgroups		Melphalan dose	Response rates		EFS/PFS/TTP		OS from transplant	
		Age group	Sample size		CR	P value	Median(months)	P value	Median(months)	P value
Merz (21)	Retrospective cohort study	60–64	83	100–200 mg/m^2	38%(nCR+CR)	NS	EFS 27	NS	Not reached	NS
		65–69	93		33%(nCR+CR)		EFS 23		Not reached	
		70–75	26		31%(nCR+CR)		EFS 23		Not reached	
Muta (11)	Retrospective cohort study	51–64	63	100–200 mg/m^2	24%	0.06	PFS 20.8	0.26	72.5	0.07
		65–76	25		12%		PFS 17.1		40.8	
El Cheikh (9)	Retrospective cohort study	60–65	104	100–200 mg/m^2	48% CR or VGPR	0.58	PFS 45	<0.0001	5 Yr OS 57%	NS
		65–77	82		41% CR or VGPR		PFS 27		5Yr OS 54%	
Kumar (22)	Matched pair analysis	37–64	60	140–200 mg/m^2	28%	NS	TTP 17.8	0.07	53.3	NS
		70–75	33		42%		TTP 28.5		Not reached	
Gertz (23)	Retrospective cohort study	≤65	541	140–200 mg/m^2	30%	NS	TTP 17	0.09	44	0.28
		>65	137		40%		TTP 17		44	
Jantunen (36)	Retrospective cohort study	39–64	79	200 mg/m^2	36%	NR	PFS 21	NS	66	NS
		65–73	22		44%		PFS 23		57	
Krejci (24)	Retrospective cohort study	31–60	103	140–200 mg/m^2	NR		NR		25.7	0.002
		66–69	30		NR		NR		71	
Terpos (37)	Retrospective cohort study	27–60	95	100–200 mg/m^2; 140mg/m^2+/−TBI	NR		NR		50.4	0.57
		61–70	32		NR		NR		37.6	
Reece (38)	Registry	30–59	382	Several doses/regimens +/− TBI	34%	NS	3Yr PFS 44%	NS	3Yr OS 55%	NS
		60–73	110		33%		3Yr PFS 35%		3Yr OS 58%	
O'Shea (39)	Retrospective cohort study	26–60	151	100–200 mg/m^2; 140mg/m^2+/−TBI	NR		NR		50.9	NS
		61–72	60		NR		NR		48.3	

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Study	Study design	Subgroups		Melphalan dose	Response rates		EFS/PFS/TTP		OS from transplant	
		Age group	Sample size		CR	P value	Median(months)	P value	Median(months)	P value
Lenhoff (25)	Population-based registry	<60	294	200mg/m^2	36%	NS	EFS 36	0.005	67	0.004
		60–64	120		37%		EFS 24		48	

ASCT, autologous stem cell transplant; EFS, event-free survival; PFS, progression-free survival; OS, overall survival; CR, complete response; nCR, near complete response; VGPR, very good partial response; NS, nonsignificant; TTP, time to progresion; NR, not reported; TBI, total body irradiation.

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Table 4

Studies of the efficacy and effectiveness of ASCT in older adults with multiple myeloma: Comparisons of autologous stem cell transplant and non-transplant treatment in older adults with multiple myeloma

		ASCT (N, age range)	Non-ASCT (N, age range)	Treatment	Median PFS (months)			Median OS (months)			
					ASCT group	Non-ASCT group	P value	ASCT group	Non-ASCT group	Hazard Ratio	P value
Present study	Retrospective cohort study	62 (65–74)	84 (65–77)	ASCT: Various induction, Mel 140–200 mg/m2 Non-ASCT: Various	NR	NR		56	33.1	0.54 (95% CI 0.35–0.82)	0.004
Facon (IFM99-06) (26)	Randomized controlled trial	N=126	MPT arm N=125 MP arm N=196	ASCT: VAD × 2, chemomobilization, Melphalan 100mg/m2 , repeated 2 months later MPT: × 12 cycles MP: × 12 cycles	19.4	MPT: 27.5 MP: 17.8	P=0.0002	38.3	MPT:51.6 MP: 33.2	NR	MPT vs MEL100 P=0.027
Lenhoff(25)	Population-based registry	120 (60–64)	97 (60–64)	ASCT: VAD then ASCT and IFN alfa-2B maintenance Non-ASCT: MP +/− IFN alfa-2B	EFS 24	NR	P=0.02	48	28	Risk ratio 0.65, (95% CI 0.42–0.92)	0.02
Offidani (40)	Post-hoc analysis of Phase II trial	26 (65–75)	62 (65–91)	Non-ASCT: ThaDD × 6 cycles, then maintenance thalidomide ASCT: ThaDD × 4 then ASCT	32	29	NS	3Yr OS 82% 5Yr OS 49%	3Yr OS 66% 5Yr OS 46%	NR	NS
Kumar (3)	Retrospective cohort study	1038 (52% over age 65)		Various	NR	NR		Not reached (95%CI 5.4 years –not reached)	3.1 years (95% CI 2.5–3.7)	NR	<0.01

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		ASCT (N, age range)	Non-ASCT (N, age range)	Treatment	Median PFS (months)			Median OS (months)			
					ASCT group	Non-ASCT group	P value	ASCT group	Non-ASCT group	Hazard Ratio	P value
Ozaki (28)	Retrospective cohort study	N=17 ASCT + novel agents; N=21 conventional chemotherapy +ASCT (Age 65–70)	N=192 conventional chemotherapy; N=88 novel agents (Age 65–70)	Various				Not reached	57.9 months		<0.001

ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival; NS, nonsignificant; NR, not reported; MPT, melphalan, prednidone and thalidomide; MP, melphalan and prednisone; VAD, vincristine, doxorubicin and dexamethasone; IFN, interferon; ThaDD, thalidomide, pegylated liposomal doxorubicin and dexamethasone.