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Autologous stem cell transplantation is safe and effective for fit older myeloma patients: exploratory results from the Myeloma XI trial

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Abstract

Autologous stem cell transplant (ASCT) remains standard of care for consolidation after induction therapy for eligible newly diagnosed myeloma patients. In recent clinical trials comparing ASCT to delayed ASCT, patients aged over 65 were excluded. In real-world practice stem cell transplants are not restricted to those aged under 65 and clinicians decide on transplant eligibility based on patient fitness rather than a strict age cut off. Data from the UK NCRI Myeloma XI trial, a large phase III randomised controlled trial with pathways for transplant-eligible (TE) and ineligible (TNE) patients, was used in an exploratory analysis to examine the efficacy and toxicity of ASCT in older patients including analysis using an age-matched population to compare outcomes for patients receiving similar induction therapy with or without ASCT. Older patients within the TE pathway were less likely to undergo stem cell harvest at the end of induction than younger patients and of those patients undergoing ASCT there was a reduction in PFS associated with increasing age. ASCT in older patients was well tolerated with no difference in morbidity or mortality between patients aged <65 years, 65-69 and 70-75. In an age-matched population of patients including those in both the TE and TNE pathways there was a significant advantage associated with undergoing ASCT with an increase in PFS (HR 0.41, p <0.0001) and OS (HR 0.51, p <0.0001), which persisted even after adjustment for baseline covariates including those related to frailty and response to induction. These findings support the use of ASCT for selected, fit older myeloma patients.

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Introduction

Autologous stem cell transplant (ASCT) is delivered as consolidation after induction therapy for eligible newly diagnosed myeloma patients. The use of ASCT became standard of care based on several randomised controlled trials that demonstrated a progression-free (PFS) and overall survival (OS) benefit (1-4). The ongoing use of ASCT in the context of current induction treatment regimens continues to be supported by data from two recent large phase III studies (5, 6). Both these studies, however, excluded patients aged over 65. In real-world practice stem cell transplants are not restricted to those aged under 65 and clinicians decide on transplant eligibility based on individual patient fitness rather than a strict age cut off. Standard of care conditioning for ASCT consists of melphalan given at a dose of 200mg/m^2 although a lower dose of 140mg/m^2 may be delivered in the case of renal impairment and is sometimes considered by clinicians for the treatment of older patients.

The European Bone Marrow Transplant (EBMT) registry demonstrates an increase in the number of patients aged over 65 undergoing ASCT in recent years. Between 2001-2005, 2478 patients aged 65-69 underwent ASCT comprising 14.1% of transplanted patients which rose to 3860 (15.8%) in the years 2006-2010. A similar pattern was seen for those aged 70 or over, 497 (2.8%) in 2001-2005 compared to 740 (3%) in 2006-2010 (7). In this analysis there was no apparent difference in transplant related mortality (TRM) between those aged 60-64: 1.8%, 65-69: 2.1% and >=70: 2.4%. This trend is mirrored in data from the US-based Center for International Blood and Marrow Transplant Research (CIBMTR) (Sharma P et al, ASH 2019).

Two randomised studies of ASCT in older patients were conducted using dose-reduced melphalan (100mg/m^2) tandem transplantation following conventional chemotherapy induction regimens. The first study randomised patients aged 50-70 years between melphalan prednisolone (MP) and vincristine, doxorubicin and dexamethasone for two cycles followed by dose-reduced melphalan and ASCT for 2 cycles (VAD+ASCT100) (8). The use of ASCT was associated with improved event-free and overall survival. The second study randomised patients between MP, MP and thalidomide (MPT) and VAD+ASCT100. This study demonstrated an improvement in overall survival for VAD+ASCT100 vs MP but the use of MPT was superior to both approaches (9). These data supported the use of ASCT100 in the context of conventional chemotherapy induction in older patients but the combination of both immunomodulatory agent induction and ASCT was not examined.

Several previous retrospective studies have examined outcome following ASCT for patients over the age of 65 or 70 following immunomodulatory and/or proteasome inhibitor-based induction. A large retrospective study of patients treated at the Mayo Clinic, US, compared 207 patients aged 70 and over to 1765 patients aged less than 70 (10). There was no significant difference in PFS, OS or TRM between the groups. A similar analysis of patients treated in Heidelberg, Germany, found no difference between outcomes for those aged 60-64, 65-69 or 70-75 (11). Retrospective data analysis has also been used to compare ASCT and no-ASCT treatment strategies for patients over the age of 65 in small patient cohorts (12, 13). These studies support the use of ASCT in patients over the age of 65 thought to be fit, but do not address whether ASCT is preferred over conventional therapy for patients in this older age group. To our knowledge, no randomised comparison of ASCT

to no-ASCT has been undertaken in patients over the age of 65 in the current treatment landscape.

Data from the UK NCRI Myeloma XI trial, a large phase III randomised controlled trial with pathways for transplant-eligible (TE) and ineligible (TNE) patients, was used to explore the efficacy and toxicity of ASCT in older patients including analysis using an age-matched population (14, 15). Patients in the trial were randomised between induction treatments with thalidomide or lenalidomide based triplets, the same combinations in both the TE and TNE pathways. This gives the opportunity to examine outcomes for transplant-eligible patients of different ages, but also to compare outcomes for similar patients receiving the same induction therapy with or without ASCT.

Methods

Myeloma XI is a phase III, open-label, parallel-group, multi-arm, adaptive trial and recruited newly diagnosed patients of all ages. Eligible patients were aged >=18 years. The trial was designed to reflect a population as close to real-world as was considered safe. Exclusion criteria were therefore limited, but included previous treatment for myeloma (excluding local radiotherapy, bisphosphonates, and corticosteroids), previous or concurrent malignancies (including myelodysplastic syndromes), grade ≥2 peripheral neuropathy, acute renal failure (unresponsive to up to 72 hours of rehydration, characterized by creatinine >500 µmol/L or urine output <400 mL/day or requiring dialysis), and active or prior hepatitis C infection. There were separate pathways for transplant-eligible (TE) and transplant-ineligible (TNE) patients.

The trial was performed in accordance with the Declaration of Helsinki 1996, and the study was approved by the national ethics review board (National Research Ethics Service, London, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, UK). All patients provided written informed consent. The trial was registered with the EU Clinical Trials Register (EudraCT number, 2009-010956-93).

The details of trial therapy and most primary outcomes have been previously published (14, 15). In brief, patients in both pathways were randomised between a thalidomide-containing triplet (cyclophosphamide, thalidomide and dexamethasone, CTD) or a lenalidomide-containing triplet (cyclophosphamide, lenalidomide and dexamethasone, CRD). Induction treatment was given for a minimum of 4 cycles (in the TE pathway) or 6 cycles (TNE) and to maximum response, and there was an induction intensification question for those with a suboptimal response to initial induction. All TE patients were planned to undergo an ASCT. Patients in both pathways underwent a maintenance randomisation between lenalidomide (+/- vorinostat) and observation.

The choice of pathway, transplant-eligible or transplant-ineligible, was left to the local investigator based on co-morbidities and patient/clinician preference. There was no age limit for entry to the transplant-eligible pathway. Induction therapy in the transplant-ineligible pathway was administered with an attenuation of dexamethasone dosing (**Supplementary Table 1**) but was otherwise similar between pathways.

All participants in the intensive pathway, who had responded (at least MR) to induction chemotherapy were planned to go on to receive high-dose melphalan and ASCT. Peripheral blood stem cell harvest was planned to commence after the participant had completed their induction and intensification (if applicable) treatment. Stem cell mobilisation and stem cell harvest was performed according to local practice but with advice to aim for the collection of enough stem cells for at least two transplants. High-dose melphalan and ASCT were given according to local practice. Adjustment for renal insufficiency was advised. Participants with serum creatinine <200 µmol/L prior to transplant were to receive the standard dose of 200mg/m^2 whilst those with serum creatinine >200 µmol/L were to receive 140mg/m^2. There was no recommendation to reduce melphalan dose based on age in the protocol.

This is a retrospective, exploratory analysis of data from the Myeloma XI trial. For the first set of analyses patients in the TE pathway were categorised by age group <65, 65-69 and 70-75 and their baseline characteristics, treatment and harvest data summarised. PFS and OS, measured from baseline trial randomisation, were compared between age group using the Kaplan-Meier method. Comparisons were made between the allocated groups using the Cox proportional hazards model stratified by the minimisation stratification factors, excluding centre, and to estimate HRs and 95% CIs. The frequency of serious adverse events and patient deaths reported were examined to compare transplant related morbidity and mortality between age groups.

Relative survival estimates were obtained using flexible parametric survival models on the hazard scale with four degrees of freedom (16) with the same covariates included in the model. Relative survival was defined as the observed survival divided by the expected survival where the expected survival is obtained from national life tables stratified by age at diagnosis, sex and calendar year. United Kingdom life-time risk was estimated from data available from the Office for National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables).

In order to compare outcomes between patients undergoing ASCT or not, a second set of analyses were performed using an age-matched group of patients in the TE and TNE pathways. This was defined by overlap of the age distributions in each pathway and comprised the older patients within the TE pathway and younger patients within the TNE pathway but excluded the extremes in both pathways. The optimal overlap was of patients aged 64-70 within each pathway, which was chosen with the aim of maximising the number of patients in the analysis whilst achieving balance between the patients receiving ASCT (52.5%) vs those who did not receive ASCT (47.5%). Three groups are considered: 1) TE patients who underwent ASCT (TE-ASCT) 2) TE patients who did not undergo ASCT (TE-noASCT) and 3) TNE patients (who did not undergo ASCT). Trial entry characteristics of patients in the three groups were summarised. Patients were scored according to the UK Myeloma Research Alliance Myeloma Risk Profile (MRP) (17) and the proportion of patients in each of the groups compared. When analysing time to event outcomes in order to avoid a survivor or immortal time bias that would be incurred by comparing all patients within these groups from baseline, patients were only included if they remained eligible to continue in

the trial at the end of induction+/-intensification and their outcomes were measured from the end of induction+/-intensification therapy. This time point was close to ASCT date for the patient in the TE-ASCT group, but represents a common time point that could be identified in all patients to enable comparison.

To estimate the treatment effect of ASCT as compared to no ASCT in this subgroup propensity score weighting using inverse probability of treatment weights was used. Propensity score weighting is a useful tool to account for imbalance in observed confounders between groups when estimating treatment effects from non-randomised data. A propensity score is a single score that represents the probability of receiving a treatment, conditional on a set of observed covariates. The goal of creating a propensity score is to balance covariates between individuals who did and did not receive a treatment, making it easier to isolate the effect of a treatment. The propensity score was based on a patient's age, sex, WHO performance status, ISS stage and induction treatment and response after completing induction treatments. The propensity score was applied using normalised inverse probability of treatment weighting (IPTW). In IPTWs, each treated subject (ASCT) receives a weight equal to the inverse of the propensity score, and each control subject (no ASCT) receives a weight equal to the inverse of one minus the propensity score. For the IPTW analysis, probability weights were applied to these individual participant data for calculation of the survivor function estimate and partial likelihood in the Cox model. Statistical analysis was performed using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata IC v16 (StataCorp. College Station, TX).

PFS was defined as the time from the point stated above to the date of confirmed disease progression or death from any cause. OS was defined as the time from the points stated above to the date of death from any cause. Cytogenetic profiling was performed using Multiplex Ligation-dependent Probe Amplification (MLPA) and quantitative real-time PCR (qRT-PCR) (18, 19). Cytogenetic risk was defined as standard (no adverse lesions), high (presence of t(4;14), t(14;16), t(14;20), or del(17p), gain(1q)), or ultra-high risk (more than 1 adverse lesion) (20, 21). The data cut-off for inclusion in this analysis was May 31, 2019.

Results

Outcomes for transplant-eligible pathway patients by age

The 2042 patients enrolled in the TE pathway had a median age of 61 (28-75); 546 (27%) were aged 65-69 and 101 (5%) were aged 70-75 (**Table 1**). Older patients were more frequently categorised as ISS stage III and had a lower performance status than younger patients. There was no significant difference in the proportion of patients in each of the cytogenetic risk groups or the number of patients in each arm of the induction treatment randomisation between age groups. Response at the end of induction was similar across age groups.

Older patients within the TE pathway were less likely to undergo stem cell harvest at the end of induction than younger patients. The percentage of patients undergoing harvest fell from 73.5% in those aged <65, to 62.2% aged 65-69 and only 57.4% aged 70 or older (**Table 1 and Supplementary Figure 1**). The reason given for not proceeding to stem cell

harvest and subsequent transplant was more likely to be due to the clinician/patient not considering that they were fit enough to proceed in the older age groups than in the younger patients (**Table 1**).

Older patients had a lower harvest median CD34+ cell count but still had a high rate of achieving the standard cut off of $2x10^6$ CD34+cells/kg needed for one ASCT. The percentage of patients achieving this target was 95.0% in those aged <65, 90.0% aged 65-69 and 88.7% aged 70 or older. Conversely, fewer patients in the older age groups achieved the cut off of $4x10^6$ CD34+cells/kg considered adequate for two ASCTs with a reduction from 63.4% to 45.6% to 32.1% in the respective age groups.

Of the 2042 patients in the transplant-eligible pathway, 1370 (67%) received melphalan. Most patients (84.7%) received 200mg/m^2 with only 10.5% reported as receiving 140mg/m^2. The proportion receiving the lower dose increased in the older age groups with only 5.5% of patients receiving 140mg/m^2 in those aged <65 years, 19.9% of those aged 65-69 and 45.5% of those aged >70. This appeared to be due to both an increased incidence of elevated serum creatinine (>200μmol/L) in the older age groups and the systematic use of the lower dose for older patients in some centres.

Response to transplant, PFS and OS outcomes for patients of different ages within the TE pathway who underwent ASCT were compared. Patient of different ages achieved a similar depth of response at 100 days post-ASCT (**Table 1**) with an improvement in response compared to the end of induction seen in 863/1366 (63.2%) of patients overall (62.7% of those aged <65, 64.5% of those 65-69 and 63.6% of those aged over 70). The median PFS was longest for patients aged under 65 and fell with increasing age (**Figure 1**). The median PFS for those aged <65 was 50.8 months [95%CI 46.3, 54.9], for those aged 65-69 was 40.0 months [36.3, 46.0] and for those aged 70-75 was 34.4 months [27.5, 46.4]. The PFS for patients aged 65-69 was shorter than that of patients aged under 65 (HR 1.26 p=0.003). Patients aged 70 or over had a shorter PFS than the <65 age group (HR 1.57, p=0.009), but not significantly less than the 65-69 age group (HR 1.24, p=0.229). The median OS for those aged <65 was 95.5 months [95% CI 89.8, Not reached], for those aged 65-69 was 91.9 months [82.3, Not reached] and for those aged 70-75 was 76.0 months [58.7, Not reached]. There was no significant difference in the OS between any of the age groups (65-69 vs <65: HR 1.09, p=0.484. 70+ vs <65: HR 1.59, p=0.051. 70-75 vs 65-69, HR=1.47, p=0.127). The 5 year OS was 75.5% [95% CI 72.6%, 78.3%] for those aged <65, 72.7% [67.3%, 78.1%] for those aged 65-69 and 65.0% [49.5%, 80.5%] for those aged 70-75 with some evidence of dissociation of the survival curve for the 70-75 age group after 3 years. There was no strong evidence of a difference in overall survival outcome when accounting for population-level mortality risk (excess mortality hazard-rate-ratio (EHR) for OS 65-69 vs <65: EHR 0.95, p=0.736. 70-75 vs <65: EHR 1.33, p=0.368, **Supplementary Figure 2 and 3** and **Supplementary Table 2**). There was also no difference in the percentage of patients who were reported as having commenced second line therapy at the time of data cut off (<65: 43.7%, 65-69: 49.5% and 70-75: 41.8%). However there was a notable difference in the proportion of patients whose second line therapy included a second ASCT (23.8%, 9.4% and 8.7% respectively).

Survival outcomes were explored stratified by melphalan dose (**Supplementary Figure 4**). Taking the whole TE population, the 140 mg/m^2 dose of melphalan appeared to be associated with a shorter PFS compared to 200 mg/m^2 (HR=1.31, p=0.012), with no difference in OS (HR=1.29, p=0.086) (**Supplementary Figure 4A**). However, this result was confounded by age as there were more patients who received 140mg/m^2 in the older age group which was associated with inferior PFS (**Figure 1**). When examined within each of the age groups there was no difference between outcome for patients who received 140 mg/m^2 in comparison to those who received 200 mg/m^2 (Age <65: PFS HR=1.20, p=0.289. OS HR=1.35, p=0.189, **Supplementary Figure 4B**. Age 65-69: PFS HR=1.18, p=0.344. OS HR=0.97, p=0.905, **Supplementary Figure 4C**. Age 70+: PFS HR=1.35, p=0.442. OS HR=1.42, p=0.522, **Supplementary Figure 4D**).

Transplant-related morbidity and mortality was examined by comparing serious adverse events (SAEs) reported within 100 days of ASCT and deaths occurring within 100 days or 365 days in the different age groups. There were 230 SAE's which were reported within 100 days of ASCT: 172 events in 149 patients in the <65 age group (15.1% of patients), 54 events in 47 patients in the 65-70 age group (14.6%) and 4 events in 4 patients in the 70-75 age group (7.3%). Death occurred in 9 patients within 100 days of ASCT: 5 aged <65 (0.5%), 3 who were 65-70 (0.9%) and 1 who was 70-75 (1.8%). 48 Patients died within 365 days of ASCT: 34 who were less than 65 (3.4%), 11 who were 65-70 (3.4%) and 3 who were 70-75 (5.5%). These data suggest there is no significant increase in mortality or morbidity after ASCT in older patients.

Outcomes in an age-matched group of older patients comparing ASCT to no ASCT

Analysis of the TE pathway patients undergoing transplant by age does not address the question of whether, at older ages, ASCT continues to be associated with improved outcomes compared to those of an equivalent age not undergoing ASCT. In order to answer this question, an age-matched group of patients was identified as described above and shown in **Figure 2A.** At baseline, patients in both the TNE and TE-noASCT groups had higher performance status and ISS than patients in the TE-ASCT group (**Table 2**). Response at the end of induction therapy was deeper in those patients in the TE-ASCT group than the other two groups.

Older patients undergoing ASCT (TE-ASCT) had a longer median PFS than those age-matched patients not undergoing ASCT, either TE-noASCT or TNE (**Figure 2B**). The median PFS for the TE-ASCT group was 39.4 months compared to TE-noASCT 9.7 months and TNE 16.5 respectively. Comparing those patients who underwent ASCT (TE-ASCT) to those who did not (TE-noASCT or TNE) there was a significant improvement in PFS associated with ASCT (ASCT vs no ASCT HR 0.41 p = <0.0001, **Figure 2D**). The same benefit was seen in terms of OS: TE-ASCT median 84.1 months, TE-noASCT 50.9 months, TNE 60.2 months (**Figure 2C**) (ASCT vs noASCT HR 0.51, p = <0.0001, **Figure 2E**). The benefit of ASCT was independent of the subsequent use of maintenance therapy, with longer PFS and OS seen in the TE-ASCT group compared to TNE whether patients were randomised to observation or maintenance therapy (**Supplementary Figure 5**).

Where possible a frailty-surrogate score was derived for patients in each of the age-matched groups using the UK Myeloma Research Alliance Risk Profile (MRP) (17) (**Table 2**). The TE-ASCT group had more patients with a low-risk MRP score and least with a high-risk score compared to the other groups.

The apparent differences in baseline variables and end of induction responses may have confounded the comparison between groups. To compensate for this propensity score weighting with inverse probability of treatment weights was used to adjust the estimate of the treatment effect of ASCT compared to no ASCT in the age-matched group of patients. As expected, the adjustment had the effect to reduce the median PFS and OS for patients in the TE-ASCT group and increase the median PFS and OS for the patients in the other two groups as compared to the unweighted ITT analysis. After adjustment, the median PFS for the TE-ASCT group was 35.8 months compared to TE-noASCT 10.4 months and TNE 16.9 months (**Figure 3A**). Comparing the impact of ASCT vs noASCT the hazard ratio remained significant (HR 0.44, p = <0.001). The same benefit was seen in terms of OS where the median OS for the TE-ASCT group was 79.8 months compared to TE-noASCT 57.3 months and TNE 59.5 months (**Figure 3B**) (ASCT vs noASCT HR 0.53, p = <0.001). This analysis suggests that even when the measured baseline covariates were appropriately weighted their remained a significant treatment benefit of ASCT as compared to no ASCT.

Morbidity and mortality was examined by comparing serious adverse events (SAEs) and deaths reported within 100 days of end of induction (+/-intensification). 203 SAE's were reported within 100 days: 132 events in 105 patients in the TE-ASCT group (26.0% of patients), 70 events in 49 patients in the TE-noASCT group (38.0%) and 65 events in 53 patients in the TNE group (22.4%). Death occurred in 5 patients within 100 days: None in the TE-ASCT group, 2 in the TE-noASCT group (2.7%) and 3 in the TNE group (2.18%). 37 Patients died within 365 days: 9 in the TE-ASCT group (2.2%), 14 in the TE-noASCT group (10.9%) and 14 in the TNE group (5.9%).

Discussion

These results demonstrate that ASCT is safe and effective for selected, fit, myeloma patients up to the age of 75. In an age-matched population treated with similar induction therapy there was a significant benefit for progression-free and overall survival associated with the use of ASCT compared to no ASCT.

The study showed that even in a group of patients initially felt to be transplant-eligible by their treating clinician, there was a clear fall in the proportion of patients undergoing stem cell harvest and ASCT with increasing age. This likely reflects clinician enthusiasm for giving patients the option of having an ASCT, by enrolling in the TE pathway, but a subsequent realisation that they were not fit enough. Commencing intensive induction therapy and using this as a therapeutic trial of fitness before making the final decision regarding ASCT may represent a valid approach to therapy especially in the intermediate age group of those aged 65-75.

Although the median CD34+ harvest cell count was lower for older patients it is not certain whether this reflects a true difference in mobilisation. The percentage of patients

who collected enough stem cells for one ASCT ($2x10^6$ CD34+cells/kg) was very high across the age groups. It is unknown what the local investigators set as the target harvest for each patient and it may be that the target for older patients was to collect enough stem cells for one transplant rather than to also save some for a possible subsequent transplant given that by the time of relapse the older patients would have achieved an even more advanced age.

The PFS for patients in the transplant-eligible pathway aged 65-69 and those aged 70-75 was shorter than for those aged under 65. This would be expected as outcomes are known to diminish with increasing age with all myeloma therapies. There was no significant difference in OS, although the survival curves appeared to dissociate for the 70-75 age group after 3 years. To further investigate this we performed overall survival analysis corrected for population-level mortality risk and found no evidence of a difference in survival. ASCT delivery in selected older patients was safe; there was no difference in survival at 3 months or 1-year post ASCT between age groups. Indeed, there were fewer SAEs occurring within 100 days of ASCT for those in the oldest age group. This may be due to the small cohort of this age group or due to a more stringent selection for fitness in these older patients.

There was no significant difference in PFS or OS in this study when comparing patients of a similar age who received $140mg/m^2$ (due to renal impairment or clinician choice) or $200mg/m^2$ of melphalan as ASCT conditioning. This reinforces the approach of using a dose reduction of melphalan conditioning only in these selected subsets of patients, with no apparent detriment to outcomes. One previous study suggested there was increased toxicity with the higher dose in those aged over 70 years (22) but a much larger and more recent study of the EBMT Registry database reporting no significant difference in survival outcomes between the doses in the overall population, but a benefit to the use of $200mg/m^2$ in those with a suboptimal response (23). As in our study, far fewer patients received the $140mg/m^2$ dose than $200mg/m^2$ in the EBMT analysis suggesting it was only used in very selected older patients or those with renal failure.

In the Myeloma XI trial the induction therapy for TE and TNE patients was with the same triplet combination. This gave the opportunity to compare outcomes for those patients undergoing transplant with patients of the same age who did not undergo transplant but had received the same induction therapy. We performed this analysis from the end of induction (+/- intensification if given) and only included patients who would have been eligible to continue in the study to avoid survivor and immortal time bias. This comparison showed a marked improvement in PFS and OS associated with ASCT. It is important to note that this comparison between ASCT and no ASCT was not randomised and therefore remains inherently subject to bias. Selection of patients for the TE pathway of the trial was done by clinician judgement and patient's preference. We found that the older patients included in the TE pathway had a lower performance status than younger patients, whereas usually performance status increases with age. This suggests active selection of only the fittest older patients for entry into the TE pathway and consideration of ASCT. Consistent with this in the age-matched population both the TE-noASCT and TNE groups had a higher PS and ISS than the TE-ASCT patients. Unfortunately data to calculate the IMWG frailty score (24), the Revised Myeloma Comorbidity Index (R-MCI) (25) or the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) (26) was not collected within the

study. We applied the UK-MRP, an outcome score previously validated only in the TNE population, across the groups and found an increased number of patients in the TNE and TE-noASCT groups to have higher-risk MRP than in the TE-ASCT group. Additionally, the TE-ASCT group had achieved deeper responses at the end of induction. This may have impacted their outcomes irrespective of transplantation. To address this a matched analysis using inverse probability of treatment weights was performed with factors including those associated with frailty and response to induction that were different between the age matched groups. This analysis confirmed the markedly improved PFS and OS for the ASCT-TE group, suggesting this finding was not confounded by fitness or prior response. It should be noted that propensity scores only balance measured covariates as confounders, and balance in measured covariates does not necessarily indicate balance in unmeasured confounders. If unmeasured covariates are confounders, they can bias treatment effect estimates. These results should therefore be interpreted with caution.

Previous studies in younger, fitter patients under the age of 65 have demonstrated the efficacy of transplant in the era of modern therapy including studies combining proteasome inhibitors and immunomodulatory agents for all patients as induction therapy. Such approaches may now be considered more optimal than the largely immunomodulatory agent based induction delivered in Myeloma XI. In the IFM/DFCI 2009 study patients received bortezomib, lenalidomide and dexamethasone (VRD) induction before randomisation between ASCT and consolidation in the form of additional cycles of VRD, with ASCT deferred to first relapse (27). The trial demonstrated an association between improved PFS and early ASCT whilst follow up for OS is ongoing. The EMN02 trial conducted a similar comparison but in the context of CVD induction and compared the use of VMP consolidation to ASCT (6), also demonstrating a PFS advantage for 1st line ASCT. Our findings support the findings of these studies and extend this to older patients that were excluded from these trials. Sub-analysis of IFM/DFCI 2009 suggests that there is no benefit of transplant in patients achieving very deep minimal residual disease negative (MRD-) responses prior to ASCT. This is of great interest as could lead to a response adapted approach to ASCT. MRD data was collected for a subset of the patients within the Myeloma XI trial, however, there were too few patients in the age-matched population to perform this analysis. Within the last 18 months two large phase 3 studies have demonstrated the addition of daratumamb to standard induction regimens (Rd and VMP) has dramatically improved the PFS and OS for older patients (28-30). Transplant-ineligible patients were randomised into these studies, although the reason for ineligibility (age, co-morbidities) is not stated. Randomised clinical trials are therefore still warranted for older patients who are fit for transplant comparing an antibody containing regimen +/- transplant.

In summary, these findings support the use of ASCT for selected, fit older myeloma patients up to the age of 75. With effective clinician selection older patients undergoing ASCT can experience long PFS and OS, comparable to younger patients, and without any significant increase in morbidity or mortality.

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Author contributions

CP, DAC, FED designed this analysis; GJM, GHJ and FED were Chief Investigators of the Myeloma XI trial; CP, KB, JJ, MJ, GC, MFK, RGO, GJM, GHJ, FED participated in recruitment and management of patients; MFK, MTD, RGO, GJM coordinated the central laboratory investigations; CP, DAC, TM, FED analysed and interpreted the data for this analysis; CP, DAC and TM drafted the manuscript. All authors contributed to critically revising the manuscript and approved the final submitted version.

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Table 1: Baseline characteristics and treatment received for patients within the transplant-eligible pathway and by age group.

	All	Age group		
	n=2042	<65 n=1396	65-69 n=545	70-75 n=101
Baseline characteristics				
Age **Median (range)**				
	61 (28, 75)	57 (28, 64)	67 (65, 69)	71 (70, 75)
Sex **n (%)**				
Male	1221 (59.8%)	821 (58.8%)	342 (62.8%)	58 (57.4%)
Female	821 (40.2%)	575 (41.2%)	203 (37.2%)	43 (42.6%)
WHO PS **n (%)**				
0	865 (42.4%)	612 (43.8%)	205 (37.6%)	48 (47.5%)
1	732 (35.8%)	466 (33.4%)	225 (41.3%)	41 (40.6%)
2	257 (12.6%)	182 (13.0%)	67 (12.3%)	8 (7.9%)
>=3	88 (4.3%)	67 (4.8%)	20 (3.7%)	1 (1.0%)
N/A	100 (4.9%)	69 (4.9%)	28 (5.1%)	3 (3.0%)
ISS **n (%)**				
I	611 (29.9%)	440 (31.5%)	141 (25.9%)	30 (29.7%)
II	782 (38.3%)	526 (37.7%)	219 (40.2%)	37 (36.6%)
III	501 (24.5%)	331 (23.7%)	141 (25.9%)	29 (28.7%)
N/A	148 (7.2%)	99 (7.1%)	44 (8.1%)	5 (5.0%)
Cytogenetic profile[#]				
SR	475 (55.2%)	318 (54.8%)	129 (55.4%)	28 (59.6%)
HiR	273 (31.7%)	185 (31.9%)	71 (30.5%)	17 (36.2%)
UHiR	112 (13.0%)	77 (13.3%)	33 (14.2%)	2 (4.3%)
Treatment within TE pathway				
Induction randomisation treatment arm **n (%)**				
CTD	1021 (50.0%)	701 (50.2%)	273 (50.1%)	47 (46.5%)
CRD	1021 (50.0%)	695(49.8%)	272 (49.9%)	54 (53.5%)
Patients response at end of Induction (+intensification where received)				
CR	149 (7.3%)	102 (7.3%)	37 (6.8%)	10 (9.9%)
VGPR	1125 (55.1%)	769 (55.1%)	297 (54.5%)	59 (58.4%)
PR	513 (25.1%)	355 (25.4%)	137 (25.1%)	21 (20.8%)
MR	60 (2.9%)	37 (2.7%)	20 (3.7%)	3 (3.0%)
NC	16 (0.8%)	12 (0.9%)	4 (0.7%)	0 (0.0%)
PD	44 (2.2%)	30 (2.2%)	10 (1.8%)	4 (4.0%)
Unable to assess	23 (1.1%)	13 (0.9%)	8 (1.5%)	2 (2.0%)
No induction	17 (0.8%)	12 (0.9%)	5 (0.9%)	0 (0.0%)

treatment or non-protocol treatment				
Death within 60 days of initial randomisation or within 60 of intensification cycle start date	36 (1.8%)	22 (1.6%)	13 (2.4%)	1 (1.0%)
Missing	59 (2.9%)	44 (3.2%)	14(2.6%)	1 (1.0%)
Patients who underwent stem cell harvest n (%)				
Yes	1423 (69.7%)	1026 (73.5%)	339 (62.2%)	58 (57.4%)
No	565 (27.7%)	332 (23.8%)	192 (35.2%)	41 (40.6%)
Unknown	54 (2.6%)	38 (2.7%)	14 (2.6%)	2 (2.0%)
Reasons stem cell harvest not performed				
Patient Decision	129 (22.8%)	70 (21.1%)	48 (25.0%)	11 (26.8%)
Patient not fit/clinicians decision	200 (35.4%)	102 (30.7%)	81 (42.2%)	17 (41.5%)
Disease progression	70 (12.4%)	52 (15.7%)	13 (6.8%)	5 (12.2%)
Death	58 (10.3%)	33 (9.9%)	23 (12.0%)	2 (4.9%)
Allogeneic transplant	8 (1.4%)	8 (2.4%)	0 (0.0%)	0 (0.0%)
Other	100 (17.7%)	67 (20.2%)	27 (14.1%)	6 (14.6%)
Median number of CD34+ cells harvested				
x10^6/kg	4.4 (0.0, 90.2)	4.6 (0.0, 88.8)	3.8 (0.0, 90.2)	3.1 (0.0, 7.7)
Patients harvesting*:				
≥ 2x10^6/kg	1277 (93.6%)	941 (95.0%)	289 (90.0%)	47 (88.7%)
≥ 4x10^6/kg	791 (58.0%)	628 (63.4%)	146 (45.6%)	17 (32.1%)
Patients who received melphalan (% of all patients in age group)	1370 (67.1%)	993 (71.1%)	322 (59.1%)	55 (54.5%)
Dose of melphalan administered (% of all patients who received melphalan)				
70mg/m^2	1 (0.1%)	0 (0%)	0 (0%)	1 (1.8%)
100mg/m^2	14 (1.0%)	8 (0.8%)	5 (1.6%)	1 (1.8%)
140mg/m^2	144 (10.5%)	55 (5.5%)	64 (19.9%)	25 (45.5%)
200mg/m^2	1161 (84.7%)	895 (90.1%)	239 (74.2%)	27 (49.1%)
Unknown/other dose	50 (3.6%)	35 (3.5%)	14 (4.3%)	1 (1.8%)
Patients who received a melphalan dose and stem cell return (% of all patients in age group)	1366 (66.9%)	990 (70.9%)	321 (58.9%)	55 (54.5%)

Patients response post-ASCT (% of all patients who received a melphalan dose and stem cell return)				
CR	297 (21.7%)	225 (22.7%)	62 (19.3%)	10 (18.2%)
VGPR	798 (58.4%)	579 (58.5%)	186 (57.9%)	33 (60.0%)
PR	201 (14.7%)	135 (13.6%)	60 (18.7%)	6 (10.9%)
MR	4 (0.3%)	4 (0.4%)	0 (0.0%)	0 (0.0%)
PD	26 (1.9%)	19 (1.9%)	4 (1.2%)	3 (5.5%)
Unable to assess	10 (0.7%)	8 (0.8%)	0 (0.0%)	2 (3.6%)
Death up to and including 100 days post ASCT	9 (0.7%)	5 (0.5%)	3 (0.9%)	1 (1.8%)
Not available	21 (1.5%)	15 (1.5%)	6 (1.9%)	0 (0.0%)

data available for 860 of 2042 (42.1%) patients (580 of 1396 (41.5%) patients aged <65 years, 233 of 545 (42.8%) patients 65-69 years and 47 of 101 (46.5%) patients 70-75 years). % given are of those with data available.

*data available for 1364 of the 1423 patients who underwent harvest (991 of 1026 patients aged <65 years, 320 of 339 patients aged 65-69 years, 53 of 55 patients aged 70-75 years) % given are of those with data available.

Table 2 **Baseline characteristics of patients in the age-matched groups**

	All	Age-matched groups		
	n=770	TE-ASCT n=404	TE-noASCT n=129	TNE n=237
Age Median (range)				
	67.0 (64.0, 70.0)	66.0 (64.0, 70.0)	67.0 (64.0, 70.0)	68.0 (64.0, 70.0)
Sex n (%)				
Male	471 (61.2%)	264 (65.3%)	73 (56.6%)	134 (56.5%)
Female	299 (38.8%)	140 (34.7%)	56 (43.4%)	103 (43.5%)
WHO PS n (%)				
0	269 (34.9%)	160 (39.6%)	44 (34.1%)	65 (27.4%)
1	321 (41.7%)	173 (42.8%)	51 (39.5%)	97 (40.9%)
2	109 (14.2%)	41 (10.1%)	20 (15.5%)	48 (20.3%)
>=3	34 (4.5%)	7 (1.7%)	10 (7.8%)	17 (7.2%)
N/A	37 (4.8%)	23 (5.7%)	4 (3.1%)	10 (4.2%)
ISS n (%)				
I	199 (25.8%)	125 (30.9%)	29 (22.5%)	45 (19.0%)
II	318 (41.3%)	164 (40.6%)	52 (40.3%)	102 (43.0%)
III	195 (25.3%)	79 (19.6%)	43 (33.3%)	73 (30.8%)
N/A	58 (7.5%)	36 (8.9%)	5 (3.9%)	17 (7.2%)
Cytogenetic profile[#]				
SR	184 (55.9%)	86 (51.8%)	37 (57.8%)	61 (61.6%)
HiR	105 (31.9%)	55 (33.1%)	19 (29.7%)	31 (31.3%)
UHiR	40 (12.2%)	25 (15.1%)	8 (12.5%)	7 (7.1%)
Induction Randomisation Treatment				
CTD/CTDa	345 (44.8%)	194 (48.0%)	62 (48.1%)	89 (37.6%)
CRD/CRDa	425 (55.2%)	210 (52.0%)	67 (51.9%)	148 (62.4%)
MRP possible to define				
Yes	646 (83.9%)	303 (75.0%)	106 (82.2%)	237 (100%)
No	124 (16.1%)	101 (25.0%)	23 (17.8%)	0 (0%)
MRP risk (% based on those patients with all MRP data available)				
Low	430 (66.6%)	243 (80.2%)	60 (56.6%)	127 (53.6%)
Intermediate	152 (23.5%)	47 (15.5%)	26 (24.5%)	79 (33.3%)
High	64 (9.9%)	13 (4.3%)	20 (18.9%)	31 (13.1%)
Patients response post Induction (+intensification where received)				

CR	94 (12.2%)	51 (12.6%)	10 (7.8%)	33 (13.9%)
VGPR	554 (72.0%)	286 (70.8%)	97 (75.2%)	171 (72.2%)
PR	114 (14.8%)	65 (16.1%)	19 (14.7%)	30 (12.7%)
MR	8 (1.0%)	2 (0.5%)	3 (2.3%)	3 (1.3%)

data available for 329 of 770 (42.7%) patients (166 of 404 (41.1%) TE-ASCT patients, 64 of 129 (49.6%) TE-noASCT patients and 99 of 237 (41.8%) TNE patients). % given are of those with data available.

Figure Legends

Figure 1:

Outcomes for patients of different ages undergoing ASCT. (A) Progression-free survival (PFS) (B) Overall survival (OS). Age <65 years (blue); 65-70 years (red); 70-75 years (yellow).

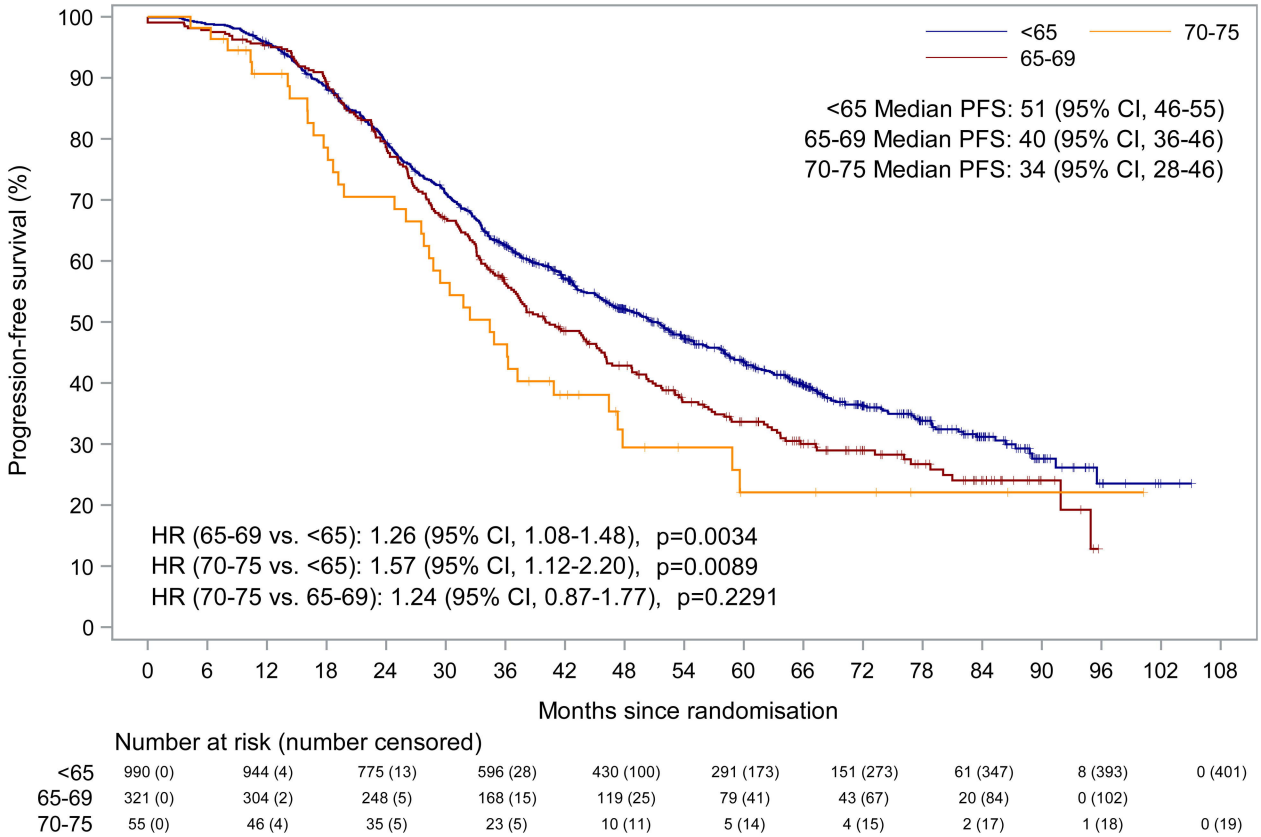
Figure 2:

Outcomes for patients in age-matched groups. (A) Histogram showing age distribution of patients in the transplant-eligible (TE) and transplant-ineligible (TNE) pathways with the overlapping patients included in the age-matched groups highlighted. (B) Progression-free survival (PFS) (C) Overall survival (OS) (D) Progression-free survival including inverse probability of treatment weighting (IPTW) (E) Overall survival outcomes of age-matched population including inverse probability of treatment weighting (IPTW).
TE-ASCT (blue), patients in the TE pathway who underwent autologous stem cell transplant; TE-noASCT (red), patients in the TE pathway who did not undergo ASCT; TNE (yellow), patients in the transplant-ineligible pathway.

Figure 3:

Outcomes for patients in age-matched groups including inverse probability of treatment weighting (IPTW). (A) Progression-free survival (B) Overall survival.
TE-ASCT (blue), patients in the TE pathway who underwent autologous stem cell transplant; TE-noASCT (red), patients in the TE pathway who did not undergo ASCT; TNE (yellow), patients in the transplant-ineligible pathway; ITT, intention to treat; IPTW, inverse probability of treatment weighting adjustment.

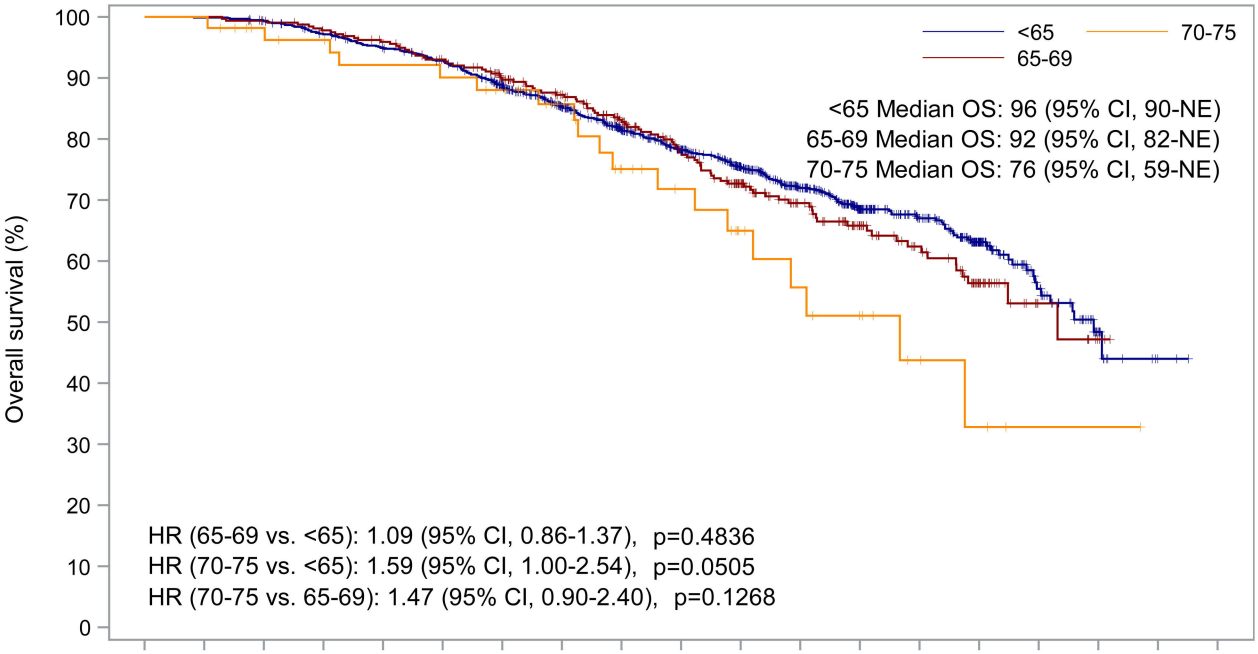
A



Number at risk (number censored)

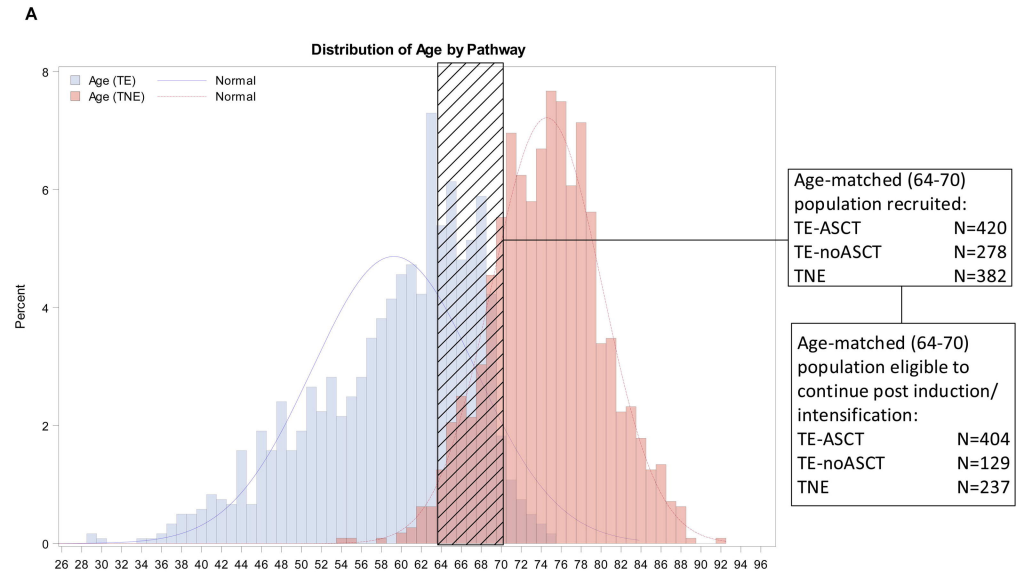
<65	990 (0)	944 (4)	775 (13)	596 (28)	430 (100)	291 (173)	151 (273)	61 (347)	8 (393)	0 (401)
65-69	321 (0)	304 (2)	248 (5)	168 (15)	119 (25)	79 (41)	43 (67)	20 (84)	0 (102)	
70-75	55 (0)	46 (4)	35 (5)	23 (5)	10 (11)	5 (14)	4 (15)	2 (17)	1 (18)	0 (19)

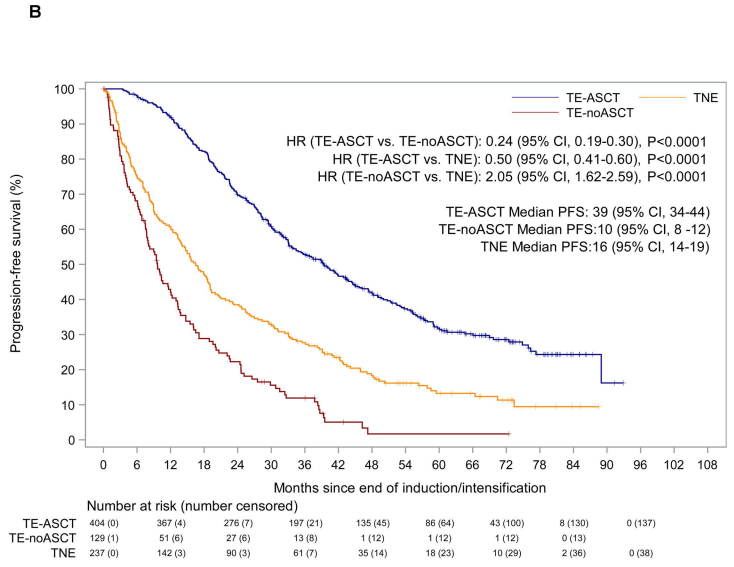
B

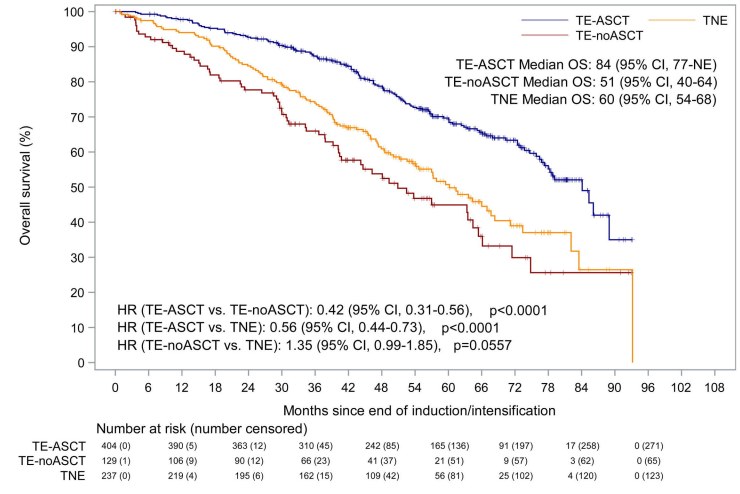


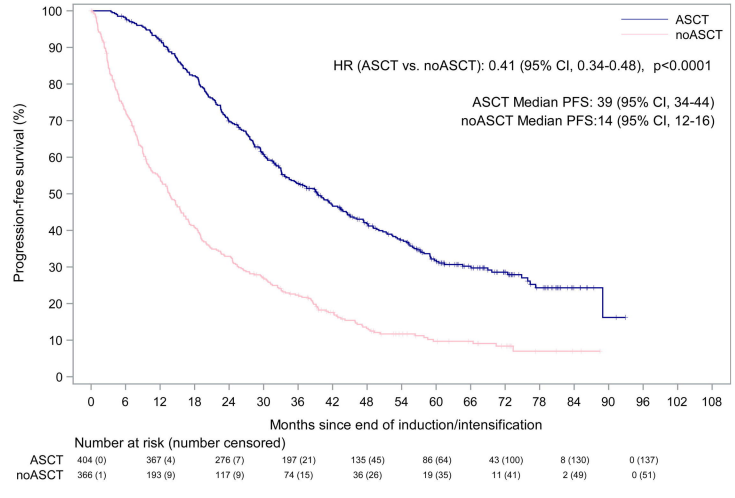
Number at risk (number censored)

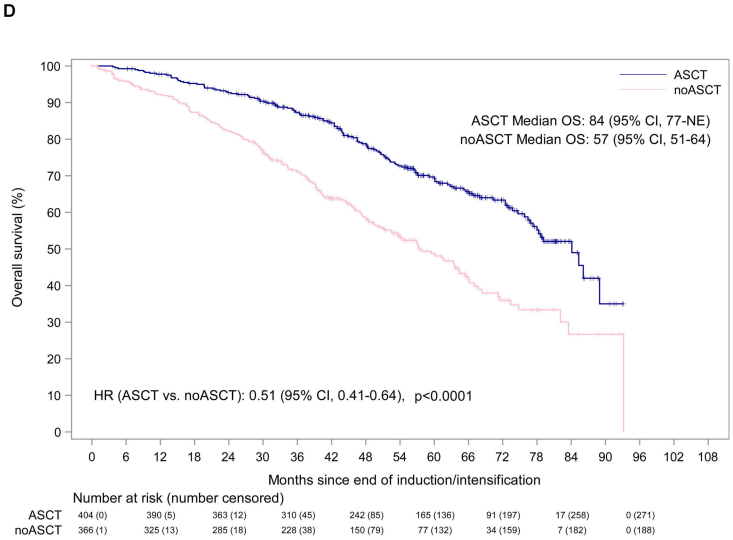
<65	990 (0)	980 (4)	924 (16)	836 (46)	674 (143)	519 (251)	292 (438)	127 (587)	15 (685)	0 (699)
65-69	321 (0)	317 (2)	300 (8)	263 (26)	214 (57)	153 (93)	87 (147)	36 (188)	3 (219)	0 (222)
70-75	55 (0)	50 (4)	45 (6)	41 (8)	26 (18)	15 (26)	9 (29)	3 (33)	1 (35)	0 (36)

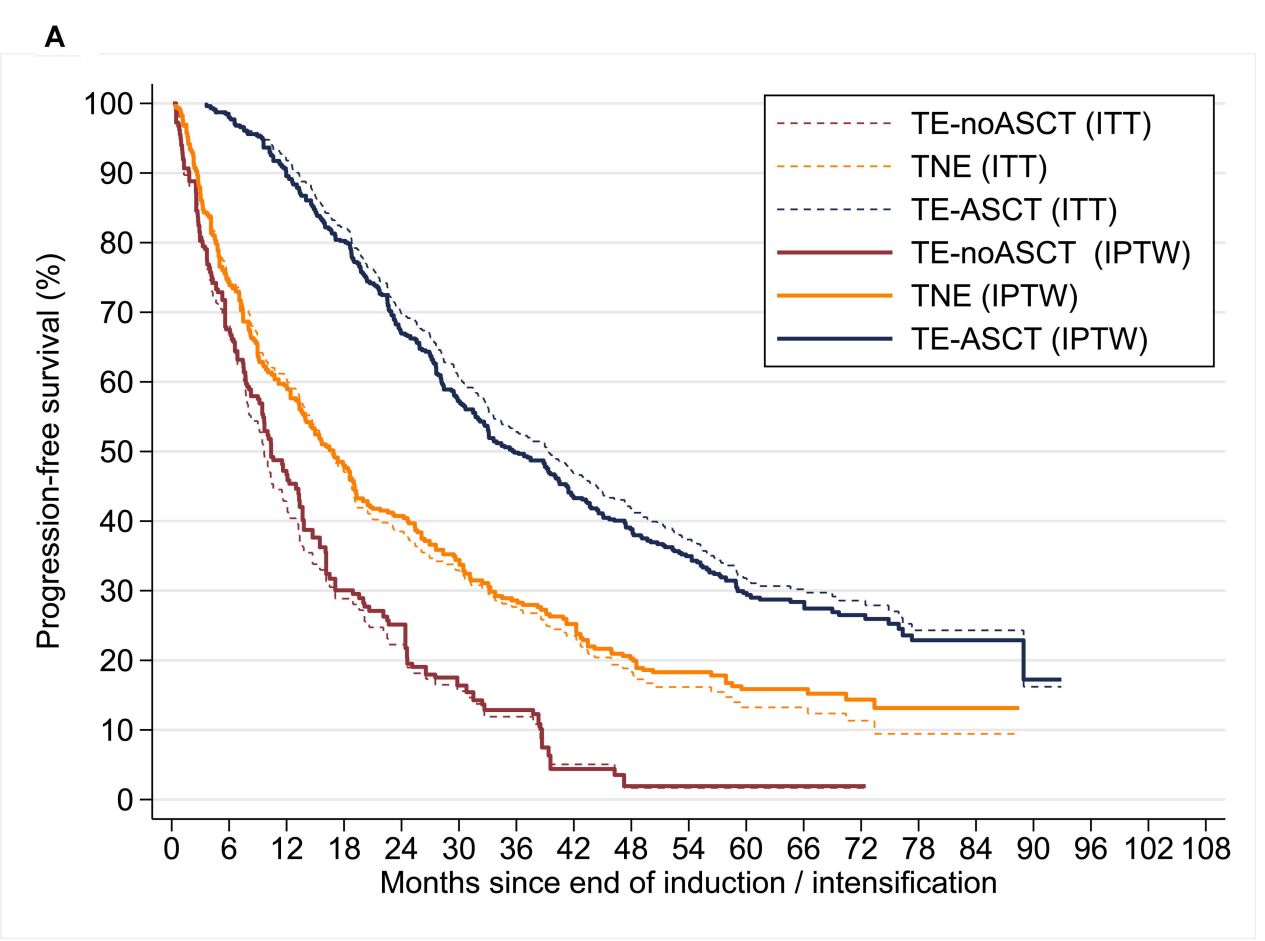

A
Distribution of Age by Pathway
Age (TE)
Age (TNE)
Normal
Normal
Percent
Age-matched (64-70) population recruited:
TE-ASCT N=420
TE-noASCT N=278
TNE N=382
Age-matched (64-70) population eligible to continue post induction/ intensification:
TE-ASCT N=404
TE-noASCT N=129
TNE N=237

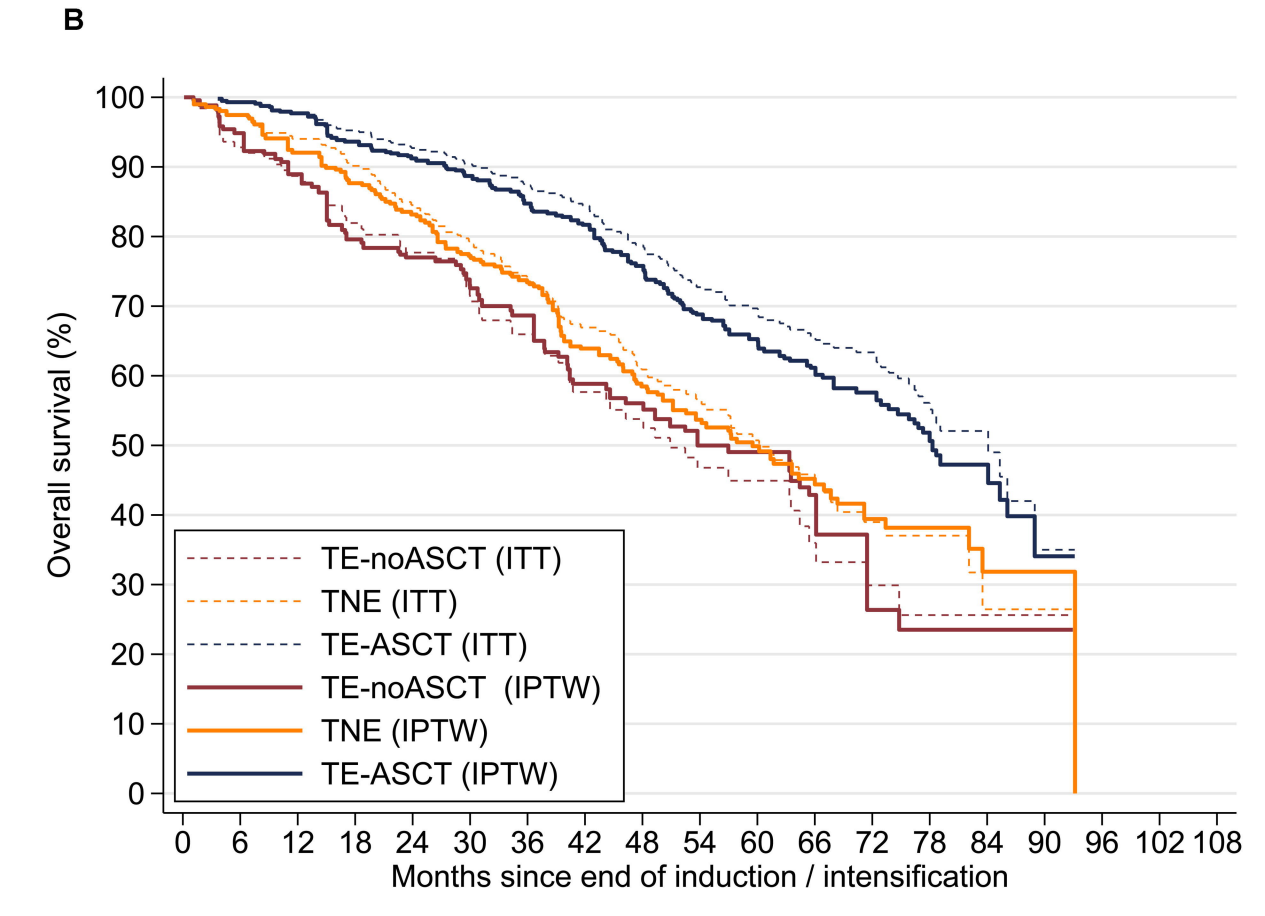

B
TE-ASCT
TE-noASCT
TNE
HR (TE-ASCT vs. TE-noASCT): 0.24 (95% CI, 0.19-0.30), P<0.0001
HR (TE-ASCT vs. TNE): 0.50 (95% CI, 0.41-0.60), P<0.0001
HR (TE-noASCT vs. TNE): 2.05 (95% CI, 1.62-2.59), P<0.0001
TE-ASCT Median PFS: 39 (95% CI, 34-44)
TE-noASCT Median PFS:10 (95% CI, 8 -12)
TNE Median PFS:16 (95% CI, 14-19)
Progression-free survival (%)
Months since end of induction/intensification
Number at risk (number censored)
TE-ASCT 404 (0) 367 (4) 276 (7) 197 (21) 135 (45) 86 (64) 43 (100) 8 (130) 0 (137)
TE-noASCT 129 (1) 51 (6) 27 (6) 13 (8) 1 (12) 1 (12) 1 (12) 0 (13)
TNE 237 (0) 142 (3) 90 (3) 61 (7) 35 (14) 18 (23) 10 (29) 2 (36) 0 (38)


C
TE-ASCT
TE-noASCT
TNE
TE-ASCT Median OS: 84 (95% CI, 77-NE)
TE-noASCT Median OS: 51 (95% CI, 40-64)
TNE Median OS: 60 (95% CI, 54-68)
HR (TE-ASCT vs. TE-noASCT): 0.42 (95% CI, 0.31-0.56), p<0.0001
HR (TE-ASCT vs. TNE): 0.56 (95% CI, 0.44-0.73), p<0.0001
HR (TE-noASCT vs. TNE): 1.35 (95% CI, 0.99-1.85), p=0.0557
Overall survival (%)
Months since end of induction/intensification
Number at risk (number censored)
TE-ASCT 404 (0) 390 (5) 363 (12) 310 (45) 242 (85) 165 (136) 91 (197) 17 (258) 0 (271)
TE-noASCT 129 (1) 106 (9) 90 (12) 66 (23) 41 (37) 21 (51) 9 (57) 3 (62) 0 (65)
TNE 237 (0) 219 (4) 195 (6) 162 (15) 109 (42) 56 (81) 25 (102) 4 (120) 0 (123)


D
ASCT
noASCT
HR (ASCT vs. noASCT): 0.41 (95% CI, 0.34-0.48), p<0.0001
ASCT Median PFS: 39 (95% CI, 34-44)
noASCT Median PFS:14 (95% CI, 12-16)
Progression-free survival (%)
Months since end of induction/intensification
Number at risk (number censored)
ASCT 404 (0) 367 (4) 276 (7) 197 (21) 135 (45) 86 (64) 43 (100) 8 (130) 0 (137)
noASCT 366 (1) 193 (9) 117 (9) 74 (15) 36 (26) 19 (35) 11 (41) 2 (49) 0 (51)


D
ASCT
noASCT
ASCT Median OS: 84 (95% CI, 77-NE)
noASCT Median OS: 57 (95% CI, 51-64)
HR (ASCT vs. noASCT): 0.51 (95% CI, 0.41-0.64), p<0.0001
Overall survival (%)
Months since end of induction/intensification
Number at risk (number censored)
ASCT 404 (0) 390 (5) 363 (12) 310 (45) 242 (85) 165 (136) 91 (197) 17 (258) 0 (271)
noASCT 366 (1) 325 (13) 285 (18) 228 (38) 150 (79) 77 (132) 34 (159) 7 (182) 0 (188)


A
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
Months since end of induction / intensification
TE-noASCT (ITT)
TNE (ITT)
TE-ASCT (ITT)
TE-noASCT (IPTW)
TNE (IPTW)
TE-ASCT (IPTW)


B
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
Months since end of induction / intensification
TE-noASCT (ITT)
TNE (ITT)
TE-ASCT (ITT)
TE-noASCT (IPTW)
TNE (IPTW)
TE-ASCT (IPTW)

Autologous stem cell transplantation is safe and effective for fit older myeloma patients: Exploratory results from the Myeloma XI trial

Contents:

Supplementary Table 1 – Dose and schedule of combination regimens in the Myeloma XI trial.

Regimen	Dose and schedule	
CRD	C: 500 mg po on days 1, 8 R: 25 mg daily po on days 1–21 D: 40 mg daily po on days 1–4, 15–18	Cycles repeat every 28 days for ≥ 4 cycles and until maximum response or intolerance
CTD	C: 500 mg po on days 1, 8, 15 T: 100 mg daily po for 3 weeks, increasing to 200 mg daily po D: 40 mg daily po on days 1–4, 15–18	Cycles repeat every 21 days for ≥ 4 cycles and until maximum response or intolerance
CRDa (attenuated-dose CRD)	C: 500 mg po on days 1, 8 R: 25 mg daily po on days 1–21 D: 20 mg daily po on days 1–4, 15–18	Cycles repeat every 28 days for ≥ 6 cycles and until maximum response or intolerance
CTDa (attenuated-dose CTD)	C: 500 mg po on days 1, 8, 15, 22 T: 50 mg daily po for 4 weeks, increasing in 50 mg increments every 4 weeks to 200 mg daily po D: 20 mg daily po on days 1–4, 15–18	Cycles repeat every 28 days for ≥ 6 cycles and until maximum response or intolerance
CVD intensification[#] (cyclophosphamide, bortezomib, dexamethasone)	C: 500 mg daily po on days 1, 8, 15 V: 1.3 mg/m^2 sc or iv on days 1, 4, 8, 11 D: 20 mg daily po on days 1, 2, 4, 5, 8, 9, 11, 12	Cycles repeat every 21 days until maximum response or intolerance (maximum 8 cycles); if CR is achieved, continue treatment for a maximum of 2 additional cycles
Lenalidomide maintenance*	10 mg daily po on days 1–21	Cycles repeat every 28 days and continue, in the absence of toxicity, until PD
Lenalidomide plus vorinostat maintenance*	R: 10 mg daily po on days 1–21 Vorinostat: 300 mg daily po on days 1–7 and 15–21	Cycles repeat every 28 days and continue, in the absence of toxicity, until disease progression

* Patients were accrued to the maintenance randomization between January 13, 2011 and August 11, 2017. Patients were initially randomized in a 1:1 ratio, using minimization with a bias element of 80%, to either R 25 mg/day (po on days 1–21 of each 28-day cycle) or observation, stratified by induction and intensification treatment. Following a protocol amendment on September 14, 2011 and after accrual of 442 patients under protocol versions 2·0–4·0, patients were randomized in a 1:1:1 ratio to R 10 mg/day (po on days 1–21 of each 28-day cycle), R plus vorinostat, or observation. Following a further protocol amendment on June 28, 2013 and after accrual of 615 further patients under protocol version 5·0, patients were randomized in a 2:1 ratio to R 10 mg/day or observation; R plus vorinostat was discontinued under protocol version 6·0. These changes were made to add research questions to this adaptive design study.

[#] Additional induction intensification therapy was administered to patients with a suboptimal response to induction therapy using a response-adapted approach: patients with stable disease (SD) after induction therapy or those with PD at any time during induction therapy received a maximum of 8 cycles of cyclophosphamide, bortezomib, and dexamethasone (CVD); patients with a minimal response (MR) or partial response (PR) were randomised (1:1) to CVD or no CVD.

Abbreviations: a, attenuated-dose; C, cyclophosphamide; CR, complete response; D, dexamethasone; iv, intravenously; PD, disease progression; po, orally; R, lenalidomide; sc, subcutaneously; T, thalidomide; V, bortezomib.

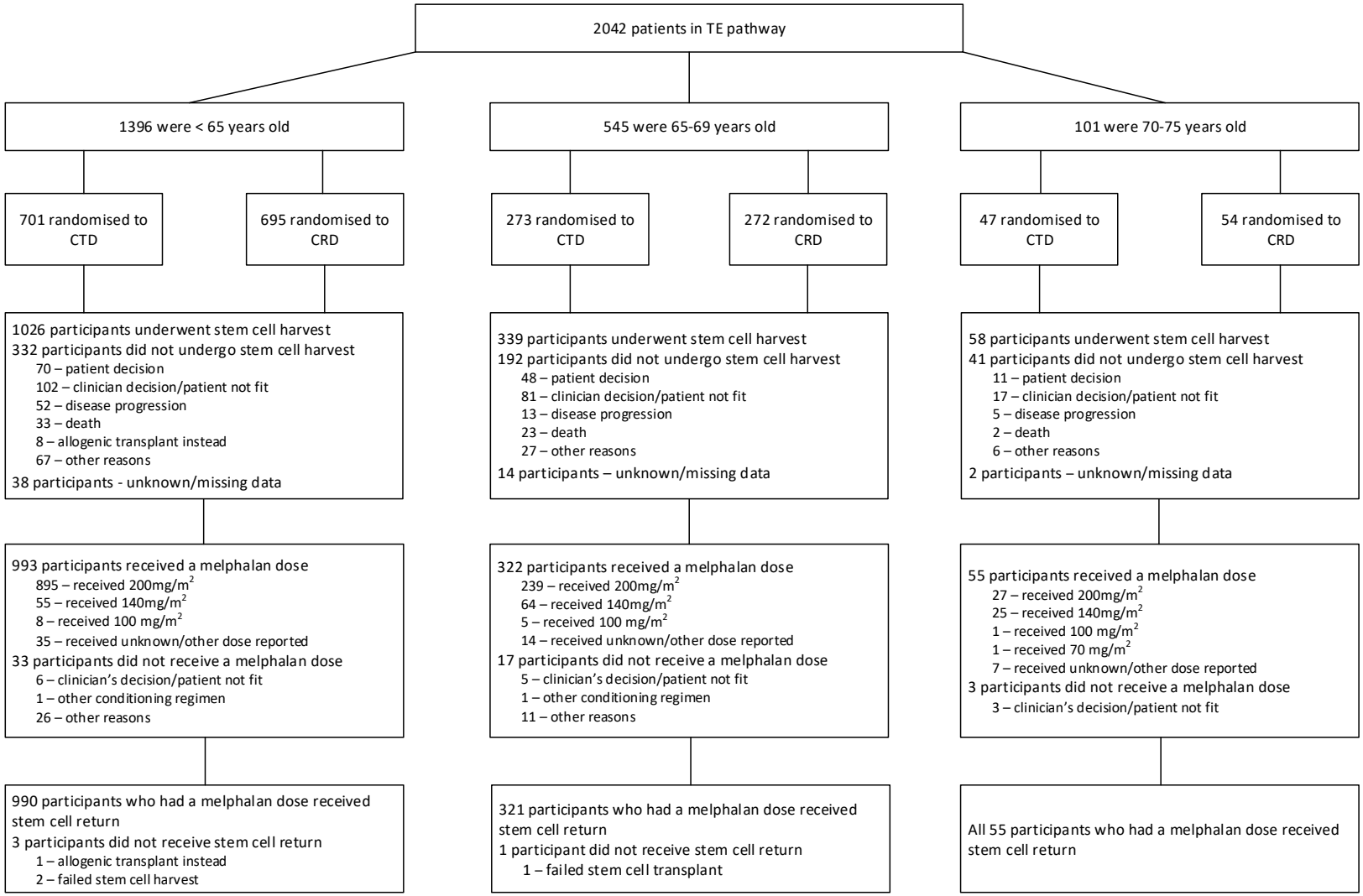
Supplementary Table 2 – Predicted relative survival analysis for patients of different ages undergoing ASCT.

Summaries at 3 months, 1 year, 2 years, 3 years, 4 years and 5 years. 95% confidence intervals (95% CI) are estimated using the delta method.

Time since randomisation	**Relative survival estimate (S*(t), %) (95% CI)**			**Excess mortality rates per 1000 person-years (95% CI)**		
	Age group			**Age group**		
	<65 years	65-70 years	70-75 years	<65 years	65-70 years	70-75 years
3 months	99.9 (99.9-99.9)	99.9 (99.9-99.9)	99.9 (99.9-99.9)	0.5 (0.0-6.0)	0.5 (0.0-5.8)	0.7 (0.1-8.8)
1 year	99.5 (99.0-99.8)	99.6 (99.0-99.7)	99.4 (98.3-99.8)	15.2 (9.5-24.3)	14.5 (8.6-24.2)	20.2 (9.4-43.5)
2 years	96.4 (95.1-97.3)	96.5 (95.0-97.6)	95.2 (90.9-97.5)	48.3 (37.6-62.0)	46.0 (33.1-64.0)	64.4 (34.0-122)
3 years	90.7 (88.9-92.3)	91.1 (88.3-93.3)	87.8 (78.5-93.3)	68.3 (53.7-87.0)	65.1 (47.2-89.7)	91.0 (48.1-172)
4 years	84.4 (81.9-86.5)	85.1 (80.9-88.4)	79.7 (65.8-88.5)	74.6 (60.4-92.1)	71.0 (52.3-96.4)	99.3 (52.6-188)
5 years	77.8 (74.9-80.4)	78.7 (73.4-83.2)	71.6 (54.0-83.5)	87.3 (72.4-106)	83.2 (62.1-111)	116 (61.8-219)

Supplementary Figure 1 – CONSORT diagram for the transplant eligible (TE) pathway of the Myeloma XI trial.

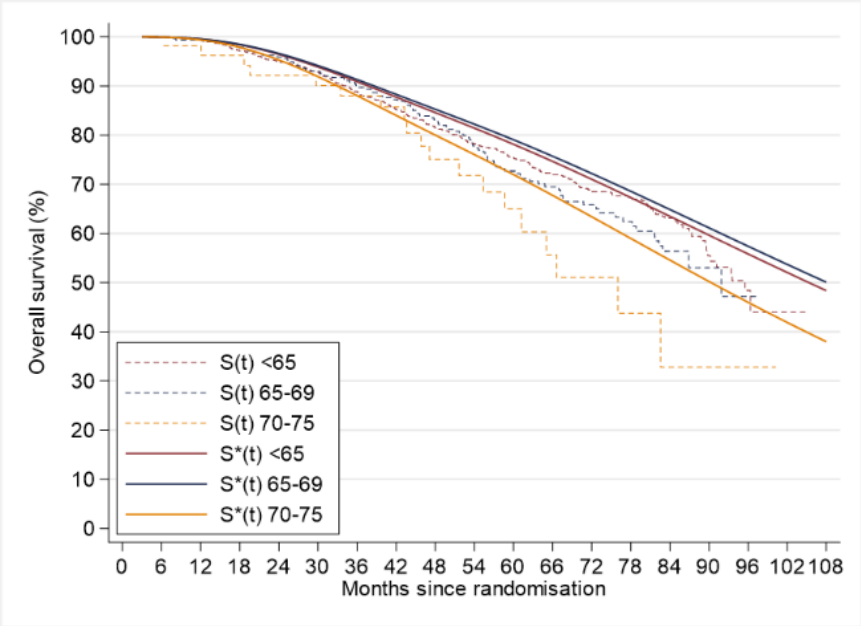
CTD, cyclophosphamide, thalidomide and dexamethasone; CRD, cyclophosphamide, lenalidomide and dexamethasone.



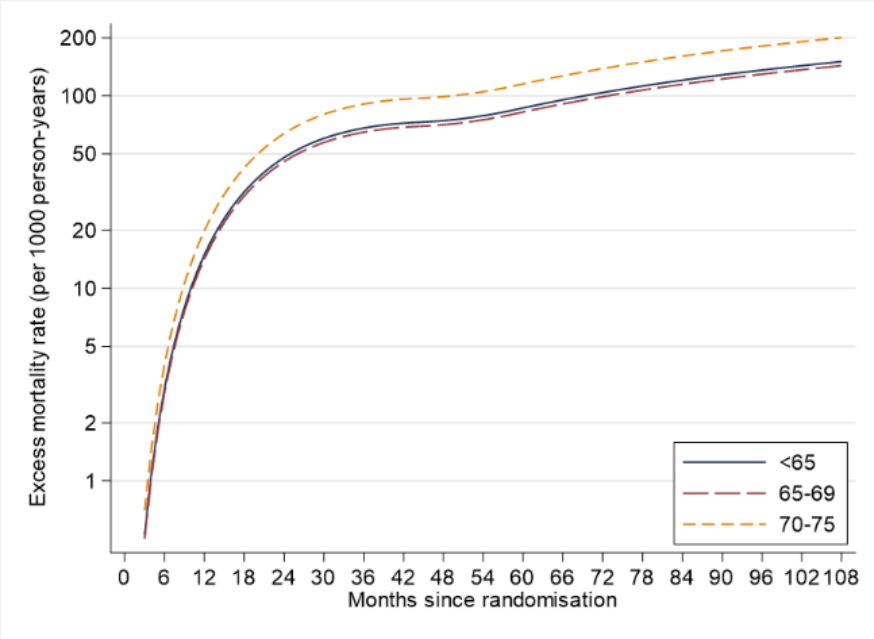
Supplementary Figure 2 – Predicted relative survival analysis for patients of different ages undergoing ASCT.

(A) Relative survivor function estimate, S*(t) accounting for population-level mortality risk (the dotted step function, S(t), is the Kaplan-Meier estimate) and (B) predicted excess mortality rates by age groups from a proportional excess-hazards model. Age <65 years (blue); 65-70 years (red); 70-75 years (yellow).

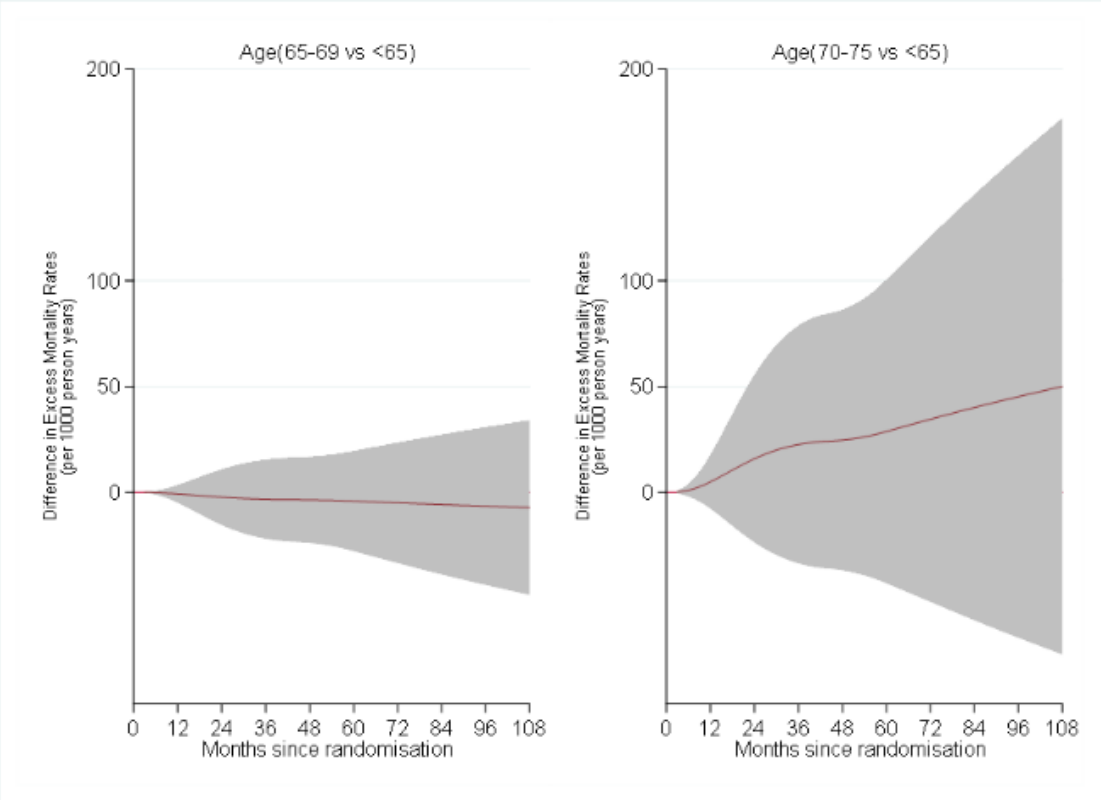
A)



B)



Supplementary Figure 3 – Difference in excess mortality rates (red lines) by age group from a proportional excess-hazards model.
The grey polygon represents 95% confidence intervals that are estimated using the delta method.

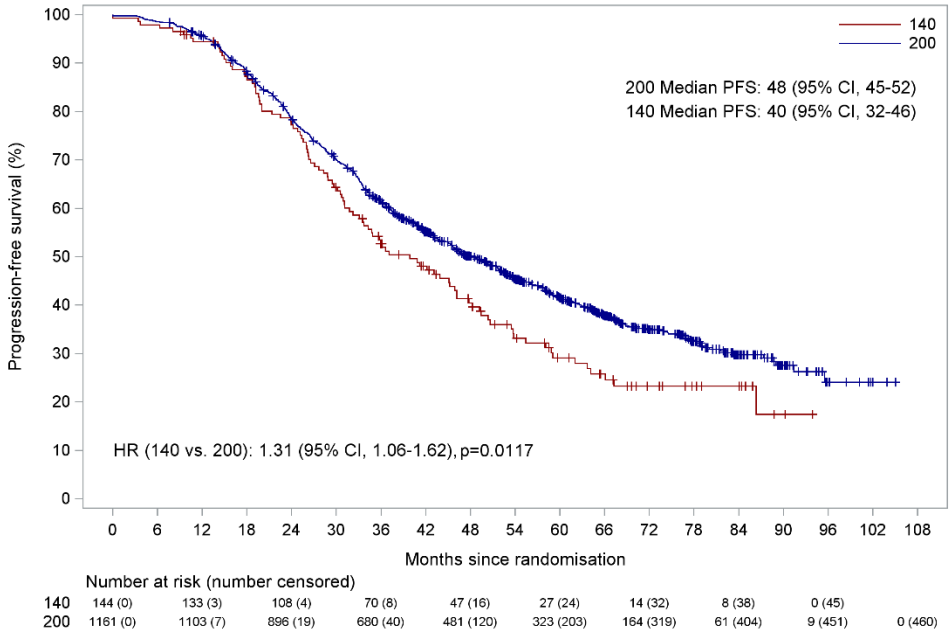


Supplementary Figure 4 – Outcomes stratified by melphalan dose 140 mg/m^2 or 200mg/m^2.

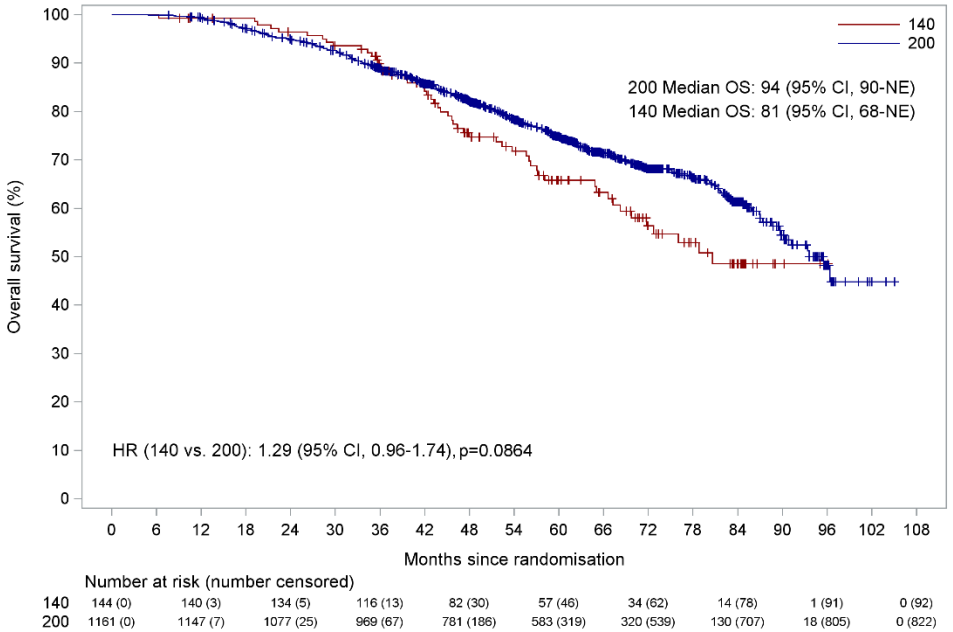
(A) the whole population, (B) age group <65, (C) age group 65-69, (D) age group 70-75.

A) Whole Population

Progression Free Survival

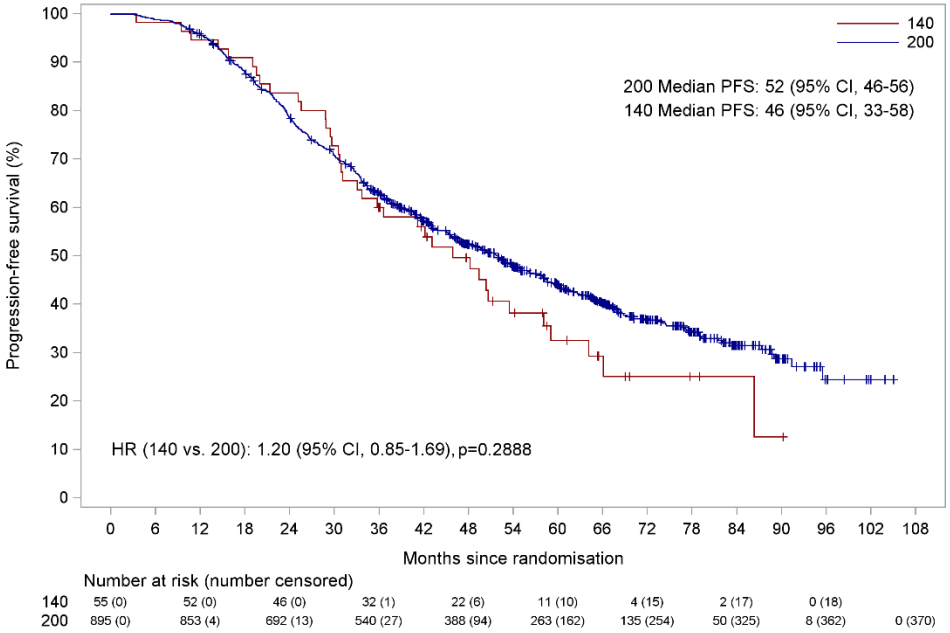


Overall Survival

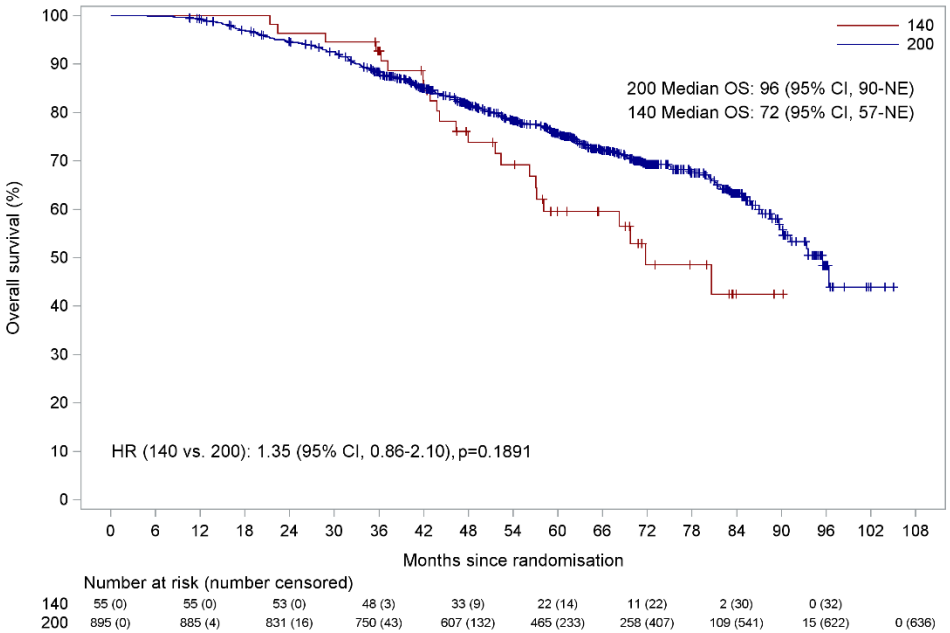


B) Age group <65

Progression Free Survival

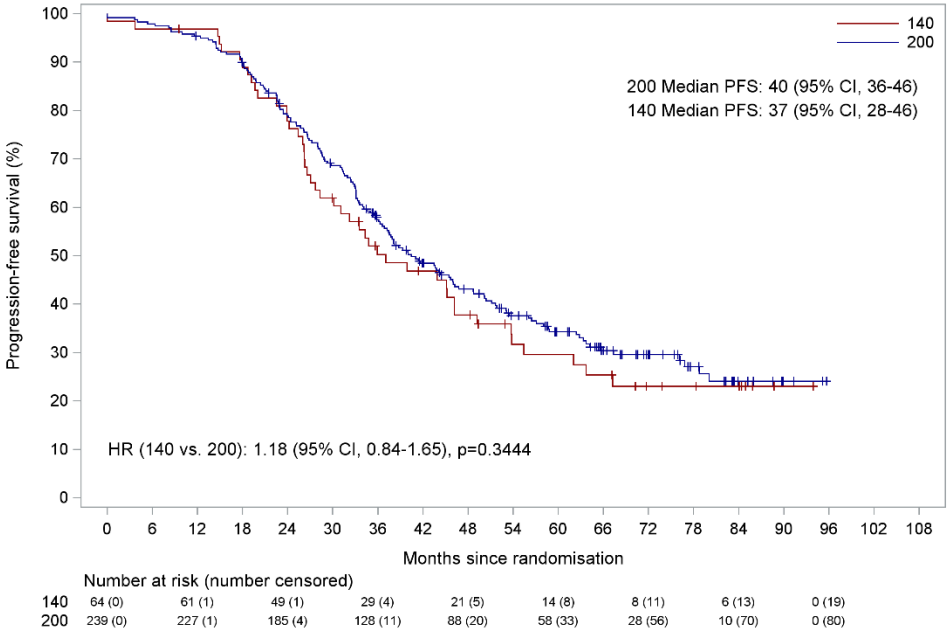


Overall Survival

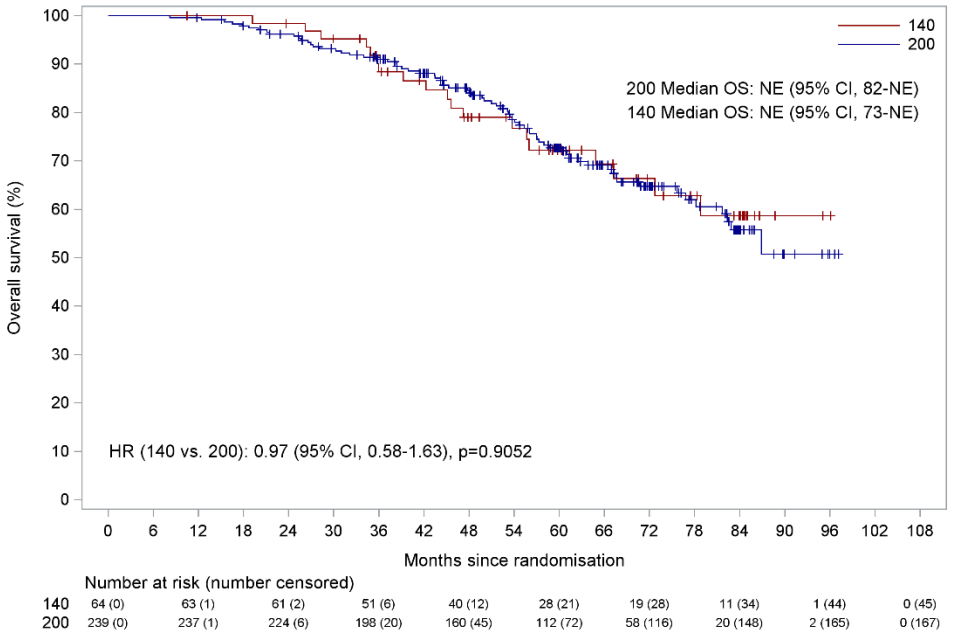


C) Age group 65-69

Progression Free Survival

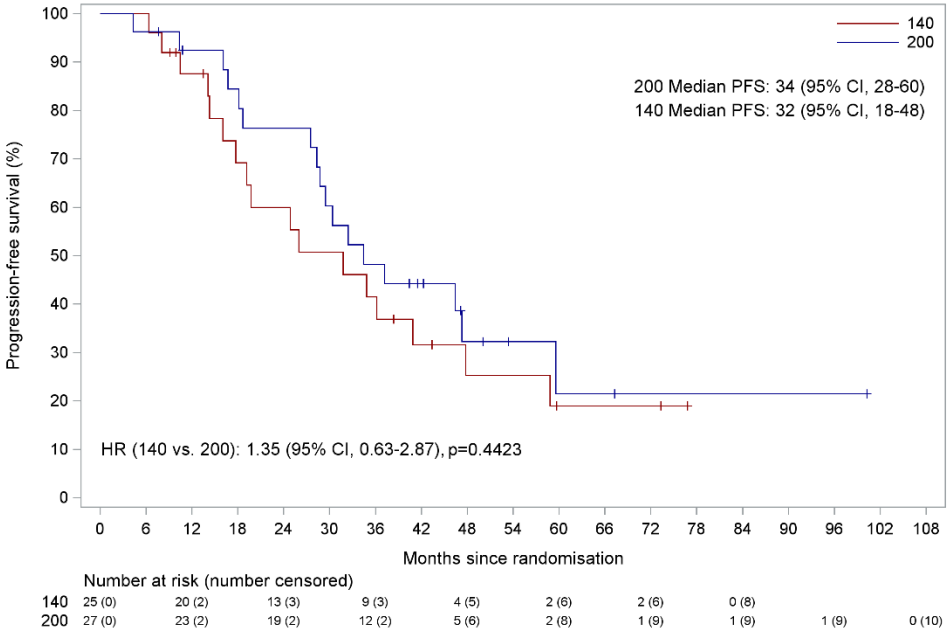


Overall Survival

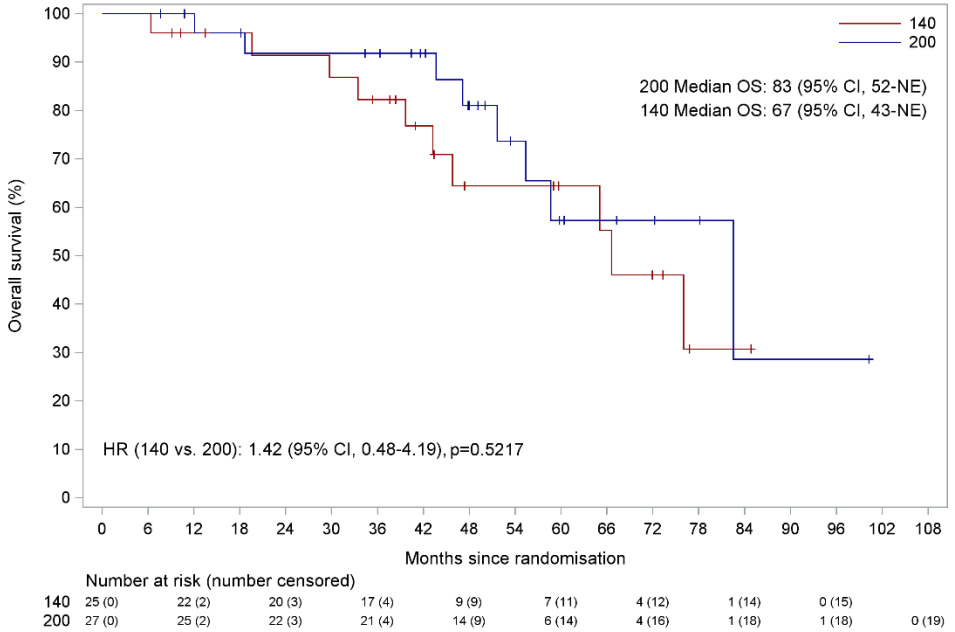


D) Age group 70-75

Progression Free Survival



Overall Survival



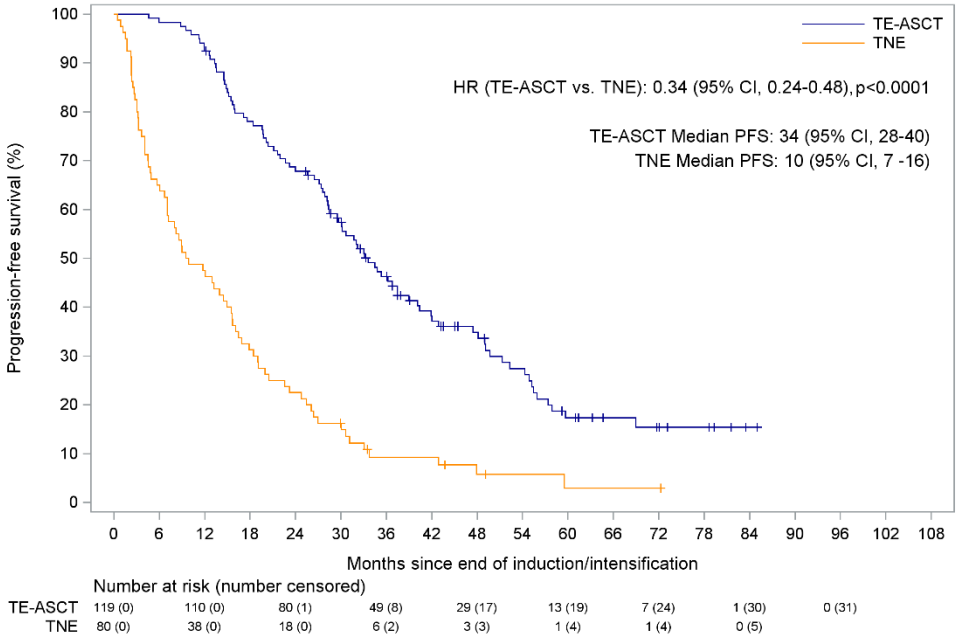
Supplementary Figure 5 – Outcomes of age-matched population by maintenance randomisation.

(A) Progression-free survival and (B) Overall survival

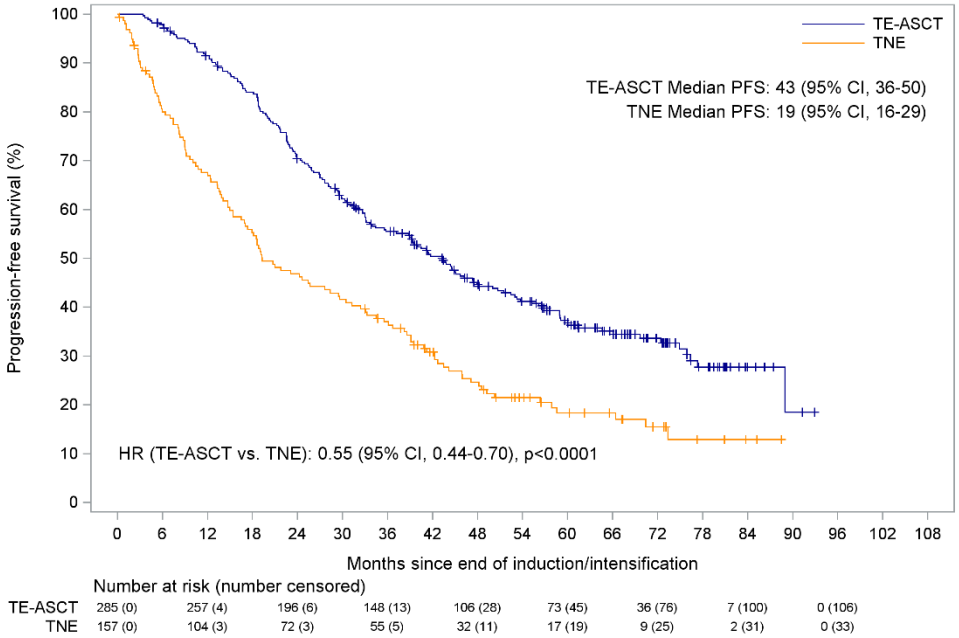
TE-ASCT, patients in the TE pathway who underwent autologous stem cell transplant; TNE, patients in the transplant ineligible pathway. This comparison cannot include patients in the TE-noASCT group as they were not eligible for the maintenance randomisation having not undergone ASCT in the TE pathway.

A) Progression-free Survival

Observation

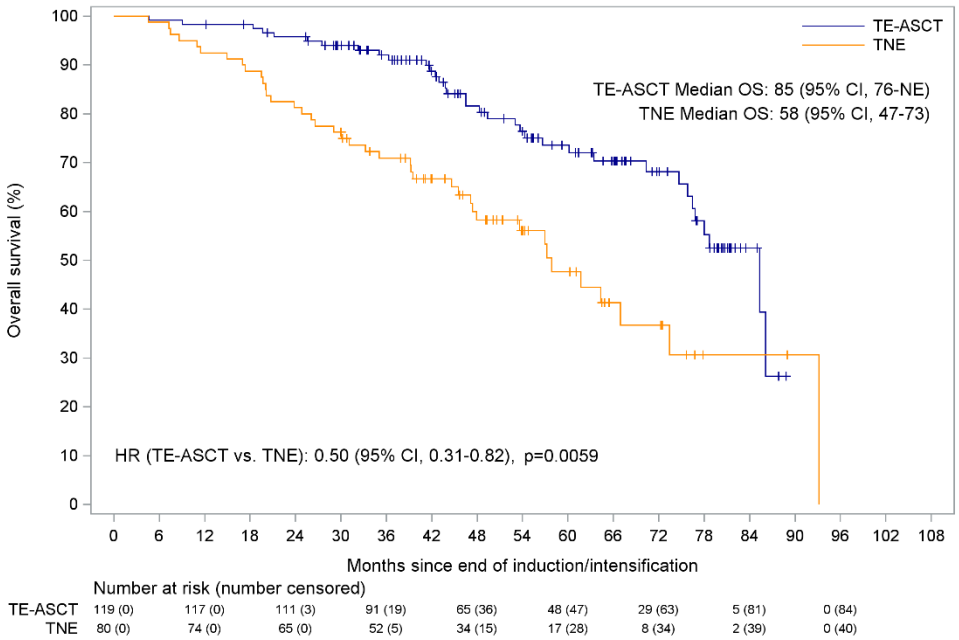


Maintenance



B) Overall Survival

Observation



Maintenance