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

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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.

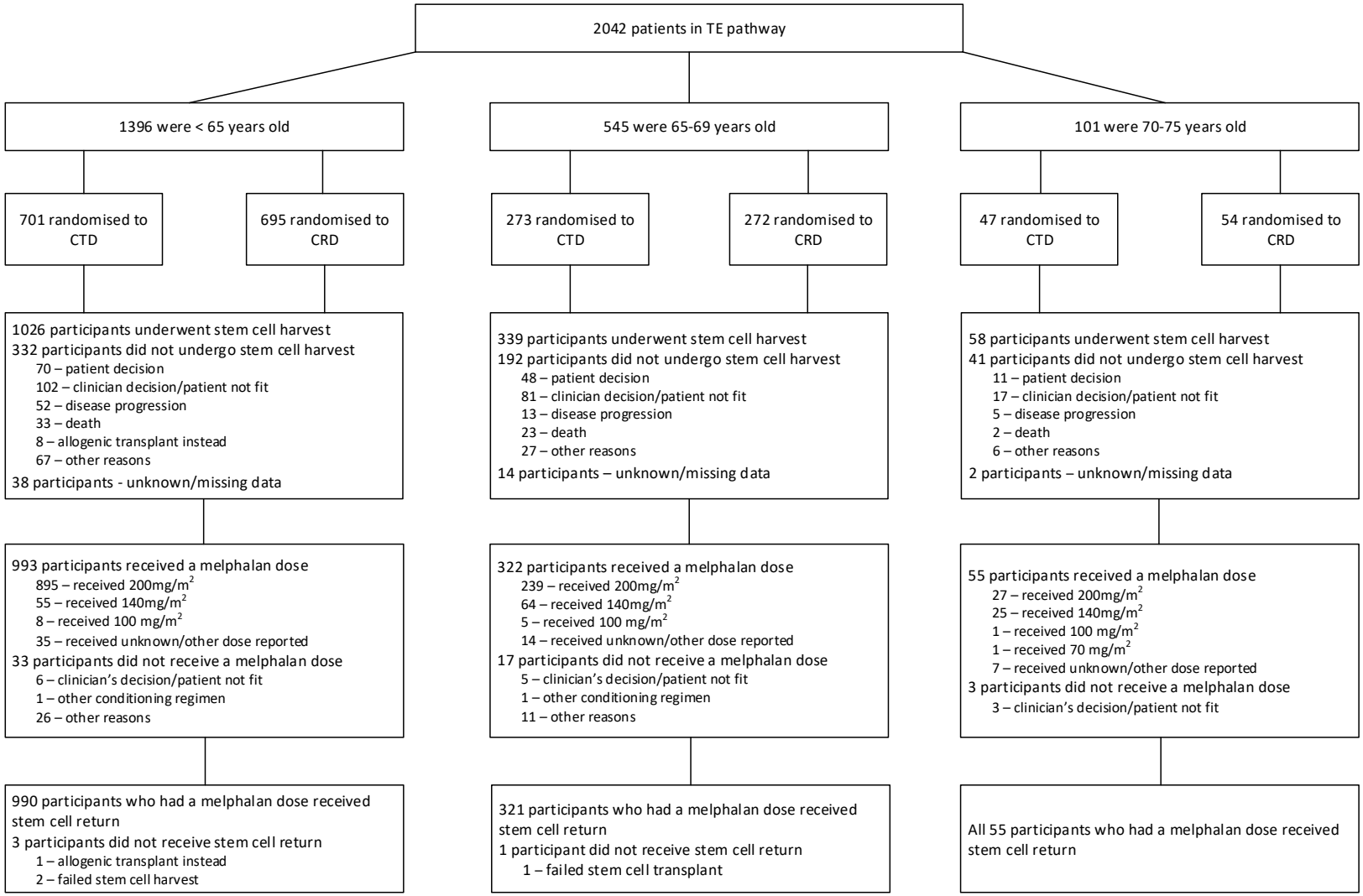
Supplementary Table 2 – Predicted relative survival analysis for patients of different ages undergoing ASCT.

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.

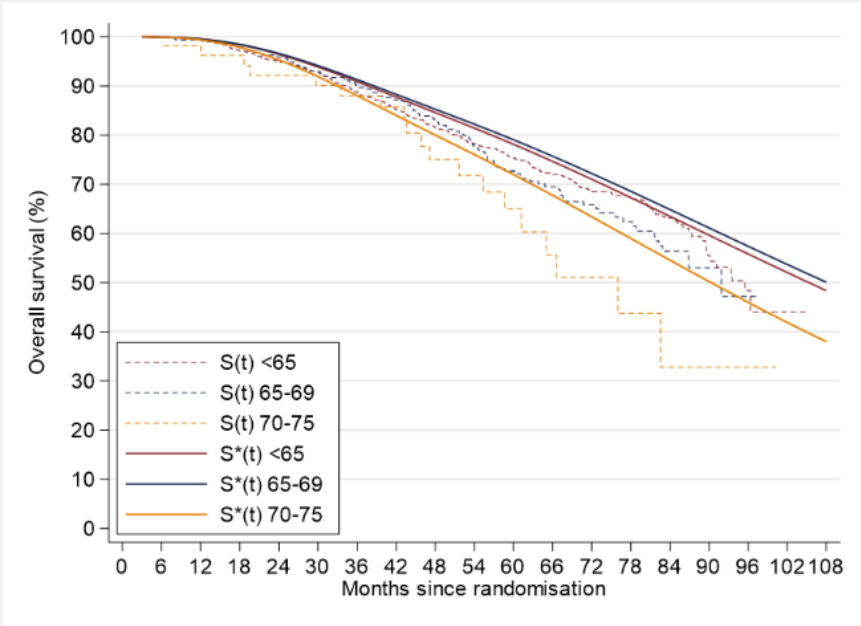
CTD, cyclophosphamide, thalidomide and dexamethasone; CRD, cyclophosphamide, lenalidomide and dexamethasone.



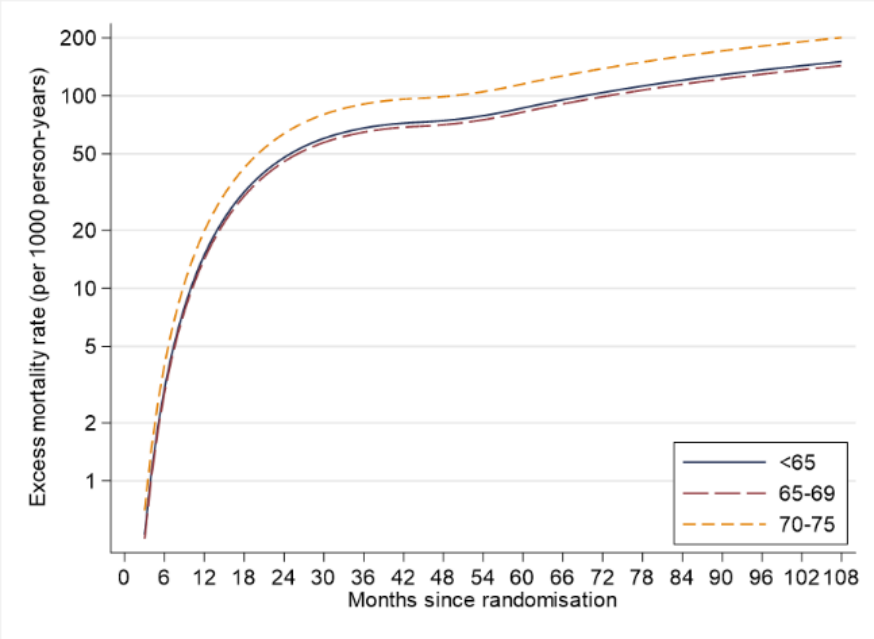
Supplementary Figure 2 – Predicted relative survival analysis for patients of different ages undergoing ASCT.

(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).

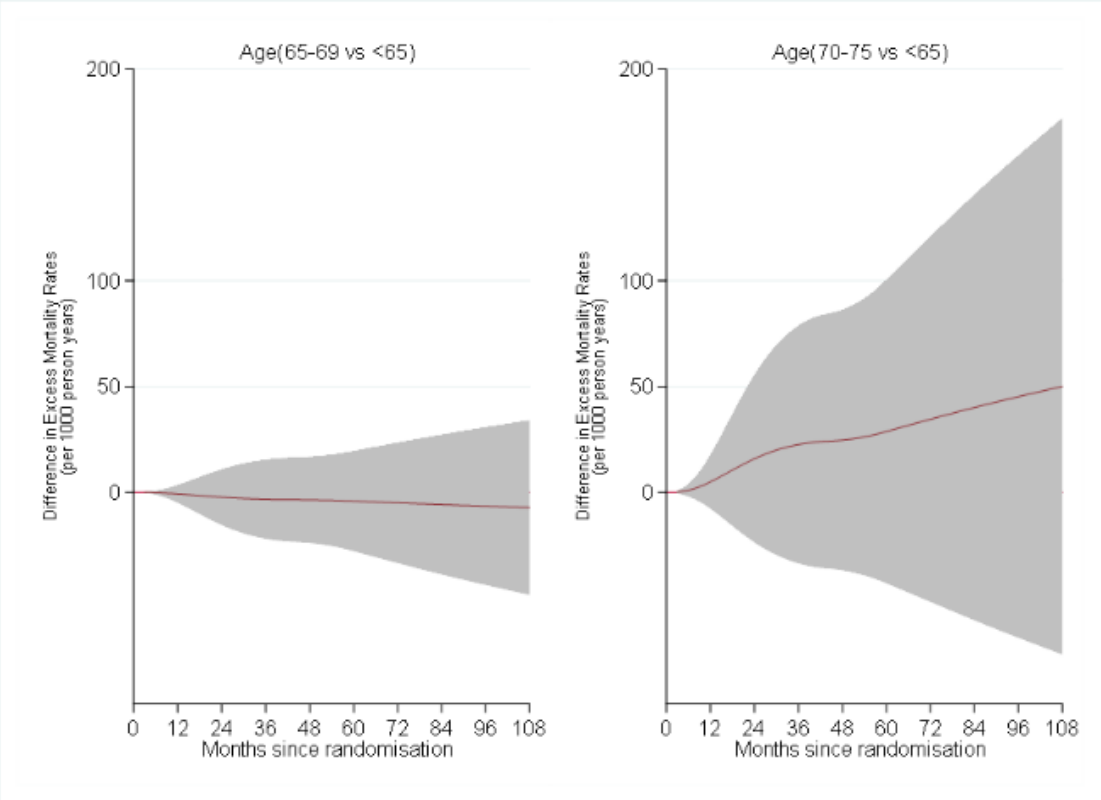
A)



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.

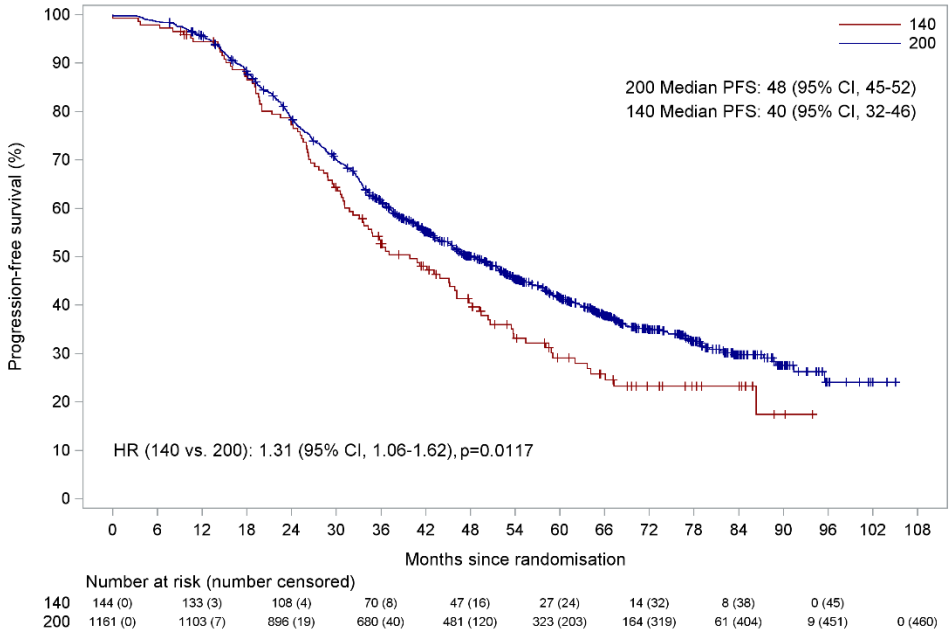


Supplementary Figure 4 – Outcomes stratified by melphalan dose 140 mg/m^2 or 200mg/m^2.

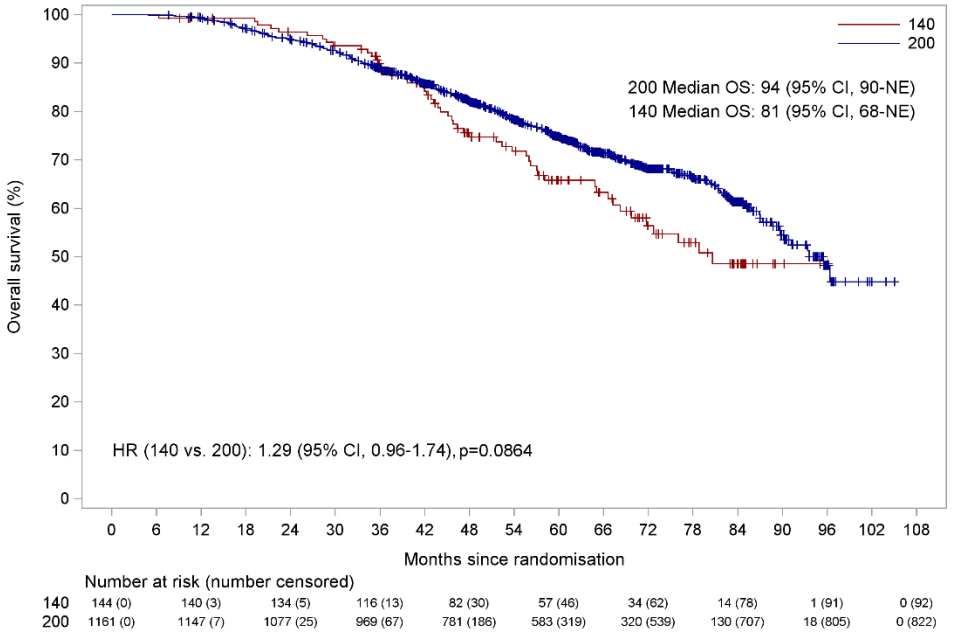
(A) the whole population, (B) age group <65, (C) age group 65-69, (D) age group 70-75.

A) Whole Population

Progression Free Survival

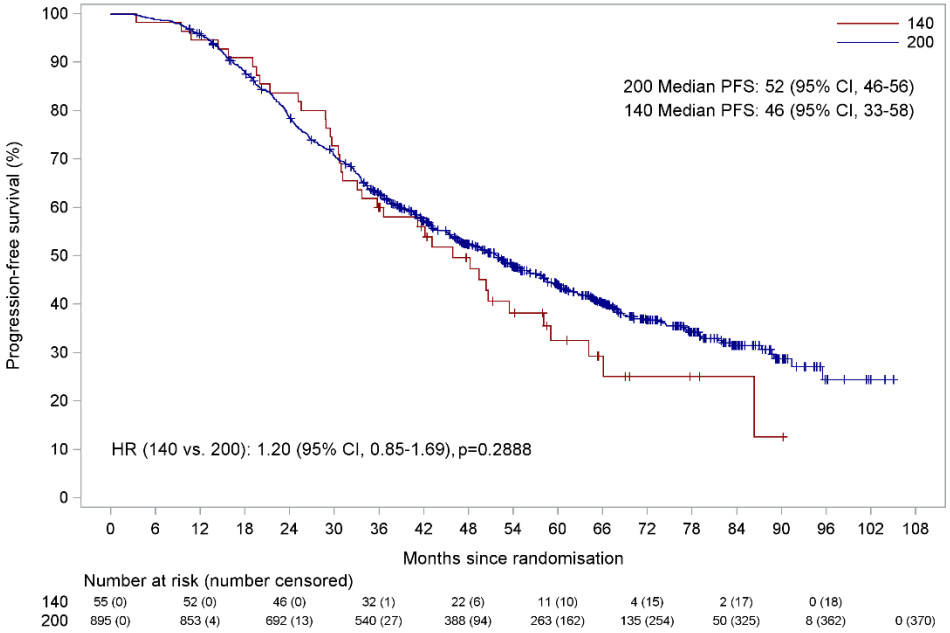


Overall Survival

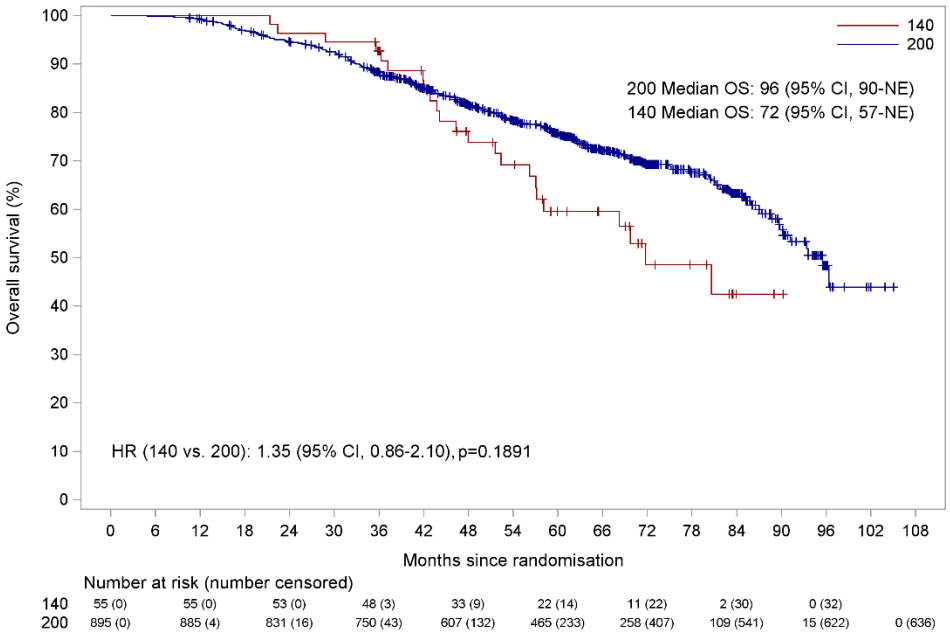


B) Age group <65

Progression Free Survival

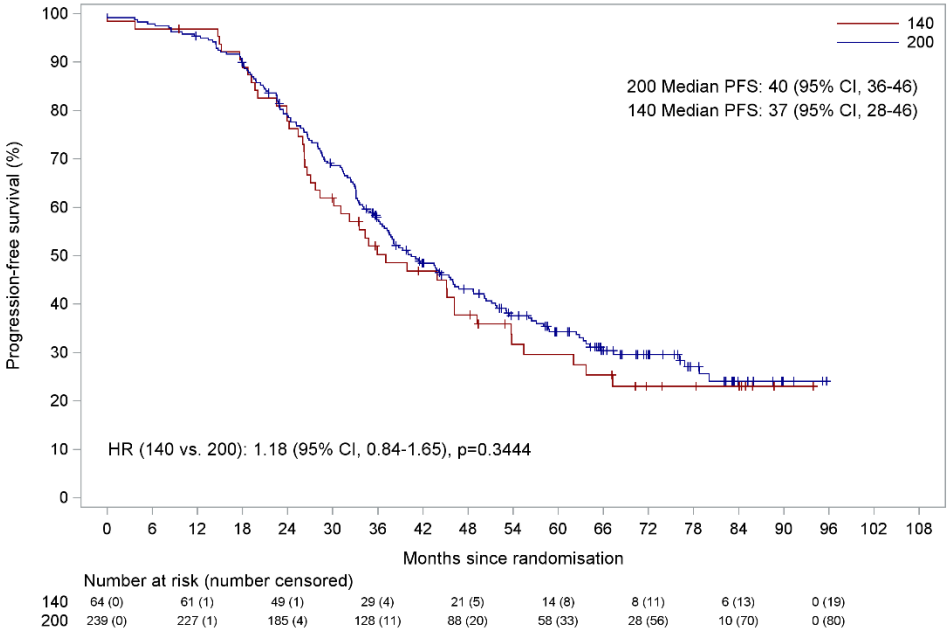


Overall Survival

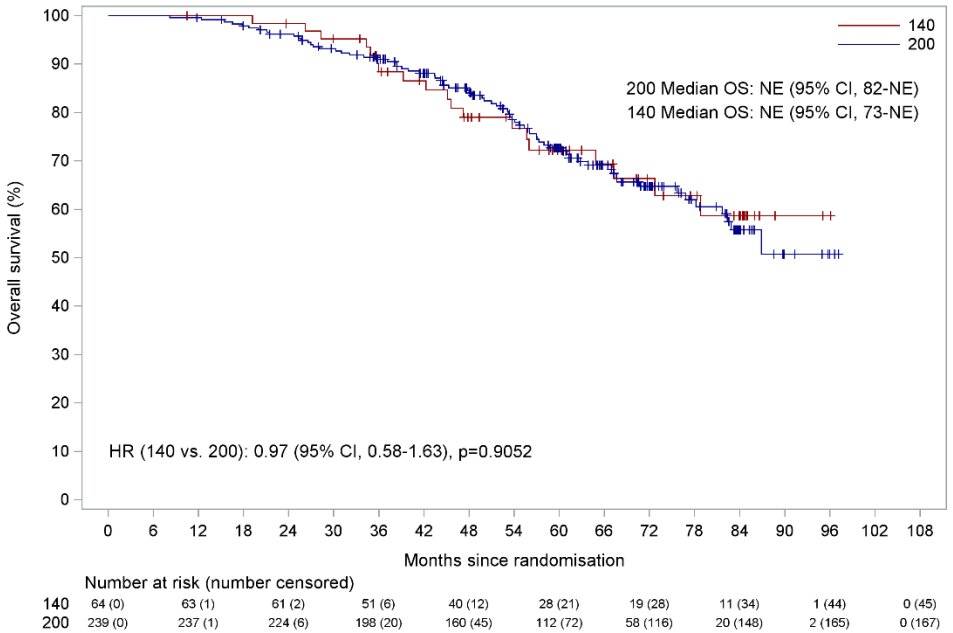


C) Age group 65-69

Progression Free Survival

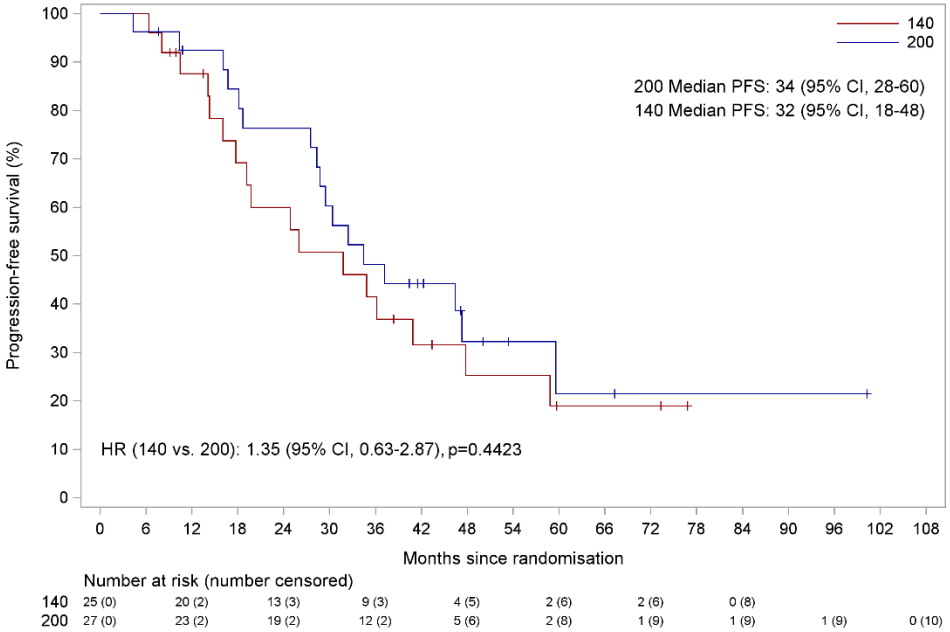


Overall Survival

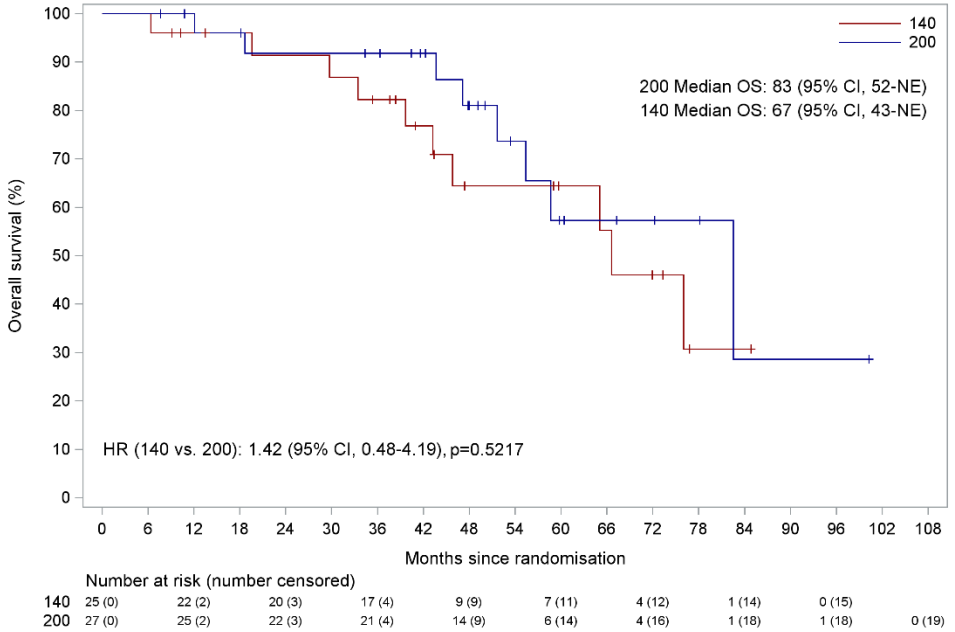


D) Age group 70-75

Progression Free Survival



Overall Survival



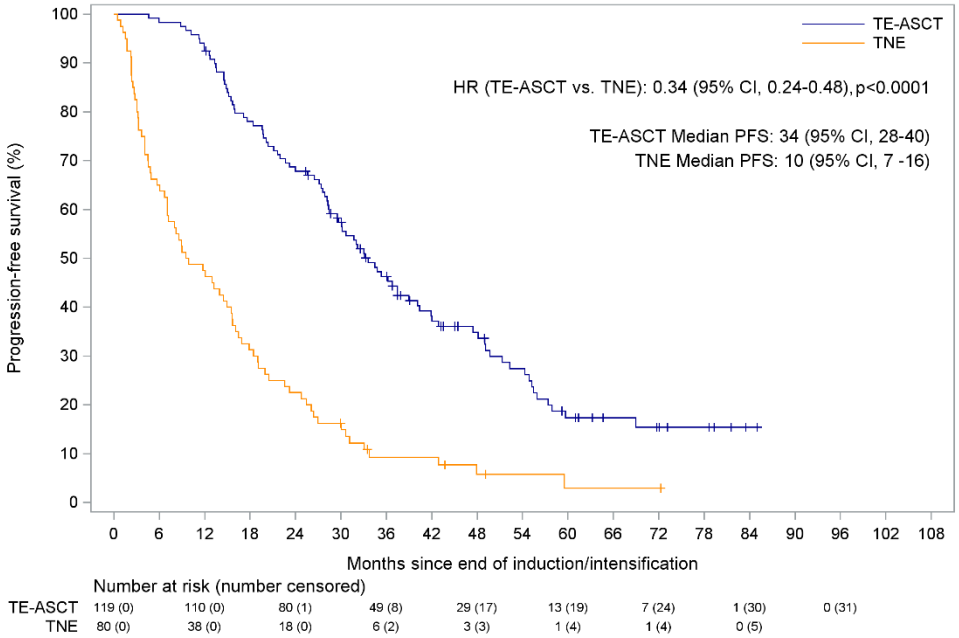
Supplementary Figure 5 – Outcomes of age-matched population by maintenance randomisation.

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

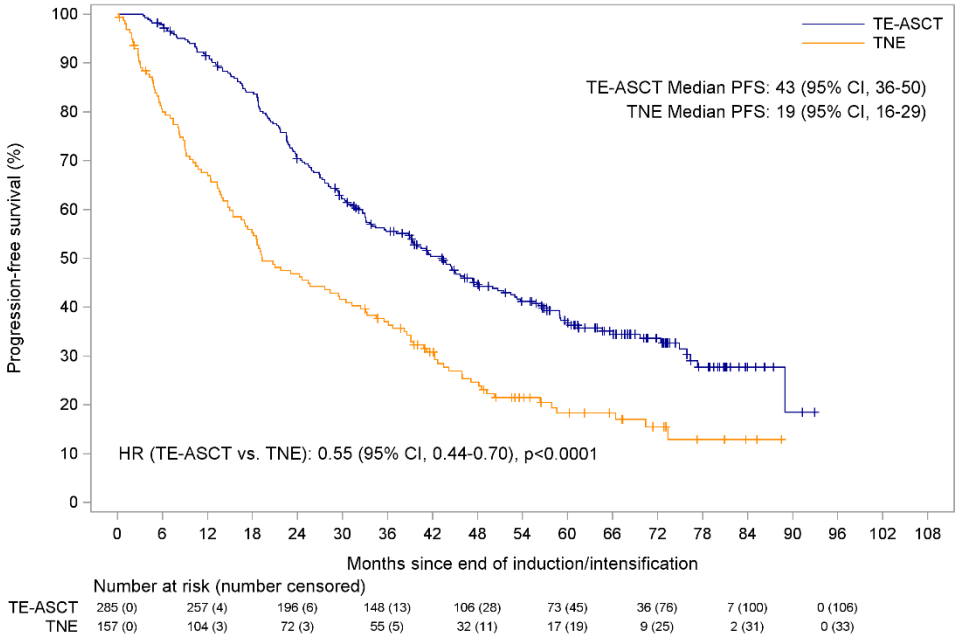
TE-ASCT, patients in the TE pathway who underwent autologous stem cell transplant; TNE, patients in the transplant ineligible pathway. This comparison cannot include patients in the TE-noASCT group as they were not eligible for the maintenance randomisation having not undergone ASCT in the TE pathway.

A) Progression-free Survival

Observation

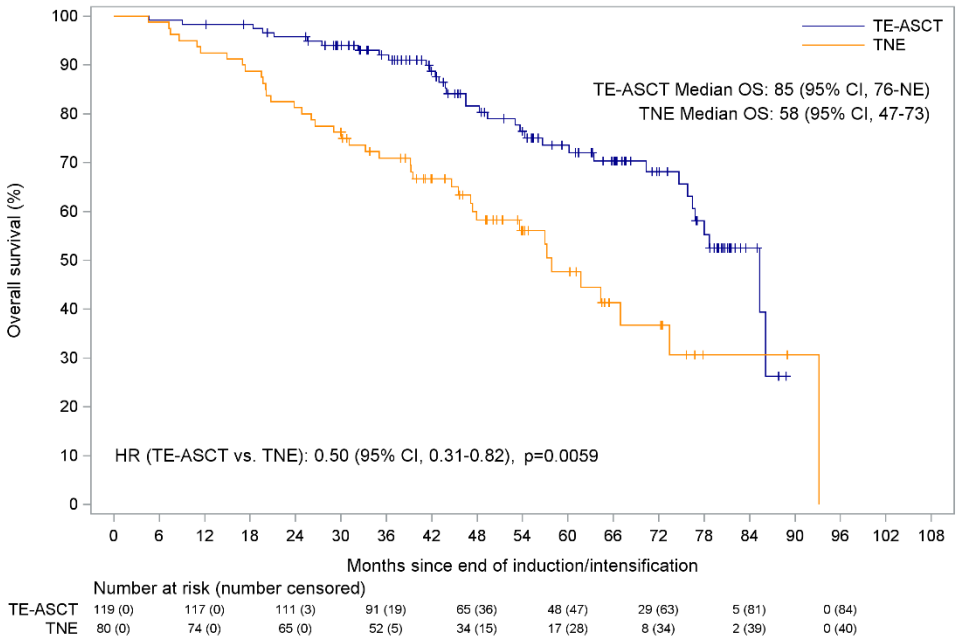


Maintenance



B) Overall Survival

Observation



Maintenance