Outcomes of relapse in patients with deferred autologous stem cell transplant after achieving at least very good partial response following bortezomib, adriamycin, dexamethasone chemotherapy for newly diagnosed multiple myeloma in the phase II PADIMAC trial

Current Phase III trials demonstrate the benefit of up-front autologous stem cell transplant (ASCT) as standard of care for transplant-eligible newly diagnosed patients with multiple myeloma.[1–3] Deeper responses and achievement of minimal residual disease (MRD) negativity with current triplet and quadruplet treatments[4] has questioned timing and role of ASCT with deferral being preferable for some.[5,6] Long-term analysis of the EMN02 trial shows that high-risk patients gain most survival benefit from up-front ASCT[3] and such risk-stratified approach to ASCT with standard risk patients receiving deferred ASCT, may be acceptable.[7] We previously reported primary results of the Phase II PADIMAC trial, which demonstrated a median progression-free survival (PFS) of 17·0 months [95% confidence interval (CI): 10·5–23·2] for 63 patients who achieved a very good partial response (VGPR) or better post induction and stopped treatment until disease progression.[8] MRD-positive patients at day 100 had a median PFS of 9·9 months (95% CI: 5·8–23·2) compared to 24·8 months (95% CI: 18·3–34·2) for MRD-negative patients. Concerns with a deferred front-line ASCT strategy include whether patients are then able to receive ASCT at relapse and if delaying ASCT is detrimental to their long-term outcomes. Here we report outcomes of patients who, having achieved at least VGPR to first-line induction therapy, followed a deferred ASCT strategy and subsequently relapsed. We describe salvage treatments and their efficacy after long-term follow-up.

Sixty-three (41·2%) of 153 newly diagnosed transplant-eligible patients enrolled on the PADIMAC trial[8] (Methods S1) achieved at least VGPR to induction and received no further treatment until disease progression. After a median follow-up of 72·2 months, 55 (87·3%) have relapsed and 24 (38·1%) have died; 32 patients (50·8%) are alive following disease progression and 7 (11·1%) are alive and progression-free. Of relapsed patients who started treatment (n = 52), 34 (65·4%) proceeded to salvage ASCT, 28 after one therapy line, with three receiving second ASCT after further relapse. Eighteen (34·6%) did not proceed to ASCT due to entry into a clinical trial or patient/physician choice (n = 8), frailty and significant co-morbidities (n = 5), inadequate or no response to salvage treatment (n = 4) and loss to follow-up (n = 1). Induction regimens prior to salvage ASCT were: 58·8% (20/34) proteasome inhibitor-based and 41·2% IMid-based (14/34) (Table SIA). For those not receiving ASCT, treatments were: 55·6% (10/18) proteasome inhibitor-based and 44·4% (8/18) IMid-based.

Overall response rate (ORR) after ASCT was 96·0% [stringent complete response (sCR) 4, CR 11, VGPR 7, PR 2, stable disease (SD) 1, not known 9]. For those not receiving salvage ASCT, ORR was 75·0% [CR 4, VGPR 6, PR 2, SD 1, progressive disease (PD) 3, not known 2]. Patients who received salvage ASCT progressed slightly earlier [median 12.1 months (95% CI: 5·819·8) vs. 16.4 months (95% CI: 7·231·1)] but had slightly longer second PFS [median 17.7 months (95% CI: 15·0–25·4) vs. 12.2 months (95% CI: 3·9–18·6)], resulting in similar PFS2 [median 40.9 months (95% CI: 27·9–59·4) vs. 40.6 months (95% CI: 16·6–63·0)]. There was weak evidence that post-relapse survival was longer for those receiving ASCT [four-year rate 57·8% (95% CI: 37·3–73·7) vs. 29·4% (95% CI: 6·3–58·1)] and suggestion towards longer OS [four-year rate 73·3% (95% CI: 54·9–85·1) vs. 59·2% (95% CI: 32·7–78·2)] (Fig 1).

Salvage ASCT patients were younger (median 52·5 vs. 60·5 years, p = 0·01); however, no difference in gender, performance status, ISS (international staging system) stage, r-ISS (revised ISS) stage, isotype, cytogenetic risk, or MRD status at peripheral blood stem cell harvest (PBSCH) or D100 (Table I) was observed. Time-to-next-treatment from first-line was similar for receiving salvage ASCT or not [median 17.9 months (95% CI: 9·7–25·0) vs. 22.0 months (95% CI: 13·3–34·5); Fig S1]. Of 34 patients who had salvage ASCT, 26 (76·5%) subsequently relapsed, and 23 (88·5%) of these started additional therapy (one died, two had not restarted). Of 18 patients who did not receive salvage ASCT, 12 (66·7%) had further relapse (one died, one developed secondary malignancy, one lost to follow-up, three had not relapsed), and 10 (83·3%) of these started subsequent therapy (Table SIB).

We report long-term outcomes of patients who achieved at least VGPR to induction and deferred ASCT. All patients accessed treatment at first relapse; however only two-thirds

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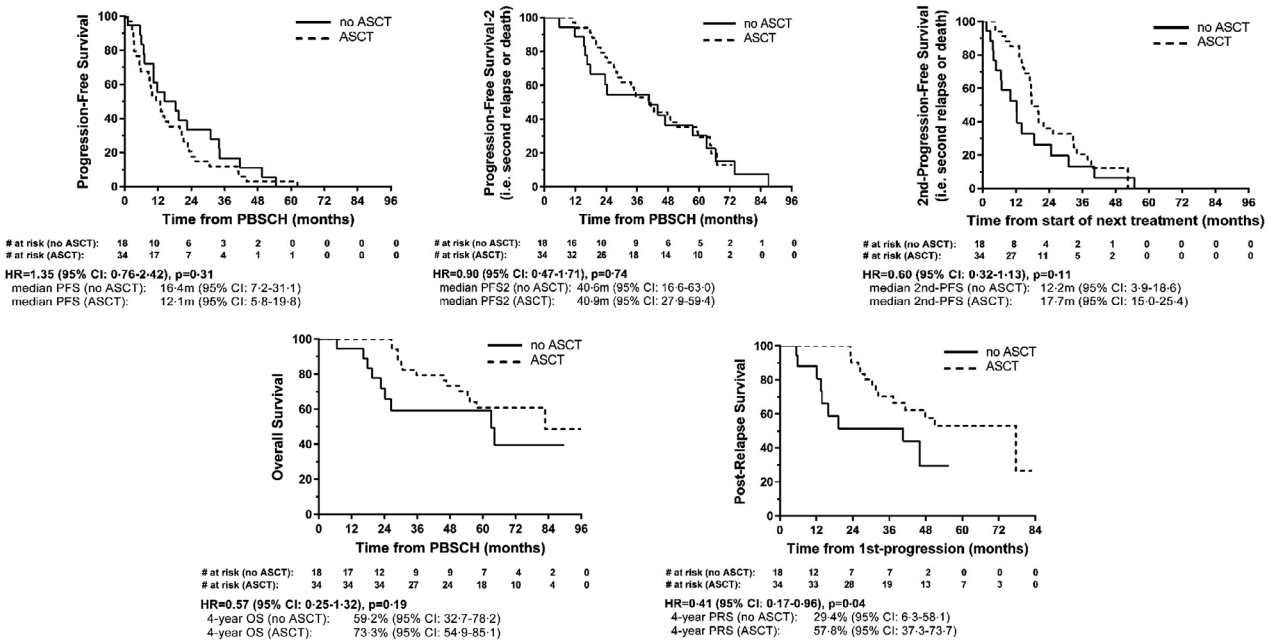

Fig 1. Outcomes by ASCT *versus* no-ASCT group. ASCT, autologous stem cell transplant; CI, confidence interval; HR, hazard ratio; OS, overall survival; PBSCH, peripheral blood stem cell harvest; PFS, progression-free survival; PRS, post-relapse survival.

(65·4%) received salvage ASCT, main reasons being patient/physician choice or frailty. If planning deferred ASCT the patient should be counselled that a significant proportion may not subsequently receive ASCT. Given patients were not randomised between salvage ASCT or not at relapse, we acknowledge potential confounders could have influenced outcomes; nevertheless we observed weak evidence for differences in long-term outcomes with lower risk of second PFS, post-relapse survival (PRS) and OS in the ASCT group. Despite this, PFS2 was similar, suggesting that non-ASCT salvage regimens were effective in disease control, though response rates were lower. Whilst all relapses were collected during patient follow-up on trial, response to subsequent treatments was collected retrospectively and some data are missing.

The EMN02 trial reported 63% of patients proceeding to ASCT after deferral.[9] The 75-month survival estimate was 69% in up-front vs. 63% deferred [hazard ratio (HR) = 0·81, $p = 0·03$]. Those with high-risk cytogenetics, particularly 17p positivity, benefitted most from ASCT.[1] The IFM2009 trial[10] reported higher rates of 79% proceeding to ASCT at first relapse. Main reason for not proceeding was disease refractoriness. At median 93-month follow-up, similar eight-year OS of 62·2% in up-front ASCT vs. 60·2% (HR=1·03, $p = 0·81$) was reported.[3] Of patients who received pomalidomide, cyclophosphamide and dexamethasone (PCD) at first relapse,[11] 94% (45/48) proceeded to salvage ASCT although patients recruited at relapse were likely fitter to proceed to ASCT. In a large cohort study, 76·7% (66/86) patients who relapsed after front-line treatment with a deferred ASCT went on to a salvage ASCT.[7] Median PFS of 143·5 months achieved in standard risk and at least VGPR response-selected patients who did not progress, reflects that a risk-stratified approach is acceptable using current consolidation and maintenance strategies.

We demonstrate approximately one-third of patients in the PADIMAC trial planned for a deferred ASCT did not receive it at relapse, and present long-term outcomes for both groups. The proportion of patients proceeding to salvage ASCT reflects that reported in other studies. When considering an up-front *versus* deferred ASCT approach, it is important to recognise that a significant number of patients may not in fact receive salvage ASCT at relapse.

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Conflicts of Interest

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Table I. Patient characteristics by no-ASCT and ASCT group.

Patient characteristics	no ASCT (n = 18)	ASCT (n = 34)	Total (n = 63*)
Age (years; median, range), p = 0·01	60·5 (43–71)	52·5 (31–67)	55·0 (31–71)
Sex, p = 0·77			
Female	8 (44·4%)	13 (38·2%)	29 (46·0%)
Male	10 (55·6%)	21 (61·8%)	34 (54·0%)
Performance status (n = 62), p = 0·28			
0	5 (27·8%)	14 (42·4%)	25 (40·3%)
1	8 (44·4%)	16 (48·5%)	29 (46·8%)
2	3 (16·7%)	1 (3·0%)	4 (6·5%)
3	2 (11·1%)	2 (6·1%)	4 (6·5%)
Isotype, p = 0·68			
IgA	8 (44·4%)	11 (32,4%)	20 (31·7%)
IgG	8 (44·4%)	19 (55·9%)	35 (55·6%)
Light chain only	2 (11·1%)	4 (11·8%)	8 (12·7%)
FISH results (n = 56), p = 0·47			
Standard risk	11 (68·8%)	26 (81·3%)	44 (78·6%)
Adverse risk	5 (31·3%)	6 (18·8%)	12 (21·4%)
ISS stage (n = 62), p = 0·56			
I	5 (27·8%)	7 (21·2%)	16 (25·8%)
II	7 (38·9%)	18 (54·5%)	29 (46·8%)
III	6 (33·3%)	8 (24·2%)	17 (27·4%)
R-ISS stage (n = 61), p = 0·80			
I	4 (22·2%)	5 (15·6%)	11 (18·0%)
II	12 (66·7%)	22 (68·8%)	40 (65·6%)
III	2 (11·1%)	5 (15·6%)	10 (16·4%)
MRD at PBSCH (n = 50), p = 0·70			
Negative	4 (44·4%)	11 (34·4%)	18 (36·0%)
Positive	5 (55·6%)	21 (65·6%)	32 (64·0%)
MRD at Day 100 (n = 50), p > 0·99			
Negative	5 (35·7%)	11 (37·9%)	18 (36·0%)
Positive	9 (64·3%)	18 (62·1%)	32 (64·0%)
Response rate to first line salvage therapy (n = 41), p = 0·07			
Overall response	12 (75·0%)	24 (96·0%)	36 (87·8%)
No response	4 (25·0%)	1 (4·0%)	5 (12·2%)

FISH, fluorescence *in situ* hybridization; ISS, international staging system; R-ISS, revised international staging system; MRD, minimal residual disease; PBSCH, peripheral blood stem cell harvest.

*Thirty-four patients had ASCT post relapse, 18 no ASCT post relapse, and 11 were excluded from ASCT *versus* no ASCT analyses (seven had not relapsed, three had relapsed but not started salvage, one patient had off-trial ASCT prior to relapse).

the study; RT: nothing to disclose; DDS: nothing to disclose; EP: nothing to disclose; JC: Janssen honoraria outside the submitted work; TA: grants from Blood Cancer UK, grants and other from Janssen, during the conduct of the study; NB: grants from Blood Cancer UK, grants and other from Janssen, during the conduct of the study; MS: Janssen honoraria outside the submitted work; SS: nothing to disclose; MK: consultancy and honoraria from Gilead and Alexion; JC: nothing to disclose; MQ: nothing to disclose; TCM: nothing to disclose; SDS: Janssen Cilag consultancy, honoraria, education grant and research funding outside the submitted work; AV: nothing to disclose; GC: grants and personal fees from Janssen outside the submitted work; CC: nothing to disclose; GP: grants and personal fees from Janssen outside the submitted work; MC: grants and personal fees from Celgene, personal fees and non-financial support from Takeda, personal fees and non-financial support from Abbvie, personal fees and non-financial support from Amgen, personal fees from Chugai, personal fees from Jazz Pharmaceuticals, personal fees and non-financial support from Janssen UK, outside the submitted work; LCH: grants from Blood Cancer UK, grants and other from Janssen, during the conduct of the study; NR: Janssen consultancy, travel support for meetings and speakers bureau outside the submitted work; RO: Janssen consultancy travel support outside the submitted work; RP: Janssen honoraria and travel support for meetings outside the submitted work; KY: Janssen honoraria and research funding.

Author Contributions

KY, RP, JC and RO conceived the study; WYC, NC, RD, RO, CR, DDS, EP, TA, NB, LCH, RP, KY analysed the data;

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Time to next treatment by ASCT *versus* no-ASCT group.

Table SI. Table of salvage treatment received.

Methods S1. Supplementary Methods.

References

1. Cavo M, Gay F, Beksac M, Dimopoulos MA, Pantani L, Petrucci MT, et al. Upfront autologous hematopoietic stem-cell transplantation improves overall survival in comparison with bortezomib-based intensification therapy in newly diagnosed multiple myeloma: long-term follow-up analysis of the randomized phase 3 EMN02/HO95 study. *Blood*. 2020;**136**(Supplement 1):37–8.
2. Gay F, Musto P, Rota Scalabrini D, Galli M, Belotti A, Zamagni E, et al. Survival analysis of newly diagnosed transplant-eligible multiple myeloma patients in the randomized forte trial. *Blood*. 2020;**136**(Supplement 1):35–7.
3. Perrot A, Lauwers-Cances V, Cazaubiel T, Facon T, Caillot D, Clement-Filliatre L, et al. Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial. *Blood*. 2020;**136**(Supplement 1):39.
4. Chim CS, Kumar SK, Orlowski RZ, Cook G, Richardson PG, Gertz MA, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia*. 2018;**32**(2):252–62.
5. Kumar SK, Buadi FK, Rajkumar SV. Pros and cons of frontline autologous transplant in multiple myeloma: the debate over timing. *Blood*. 2019;**133**(7):652–9.
6. Dhakal B, Szabo A, Chhabra S, Hamadani M, D'Souza A, Usmani SZ, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol*. 2018;**4**(3):343–50.
7. Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. *J Clin Oncol*. 2020;**38**(17):1928–37.
8. Popat R, Counsell N, de Tute R, De-Silva D, Phillips EH, Cavenagh JD, et al. Using depth of response to stratify patients to front line autologous stem cell transplant: results of the phase II PADIMAC myeloma trial. *Br J Haematol*. 2021;**193**(3):e19–22.
9. Cavo M, Gay F, Beksac M, Pantani L, Petrucci MT, Dimopoulos MA, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol*. 2020;**7**(6):e456–e68.
10. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;**376**(14):1311–20.
11. Garderet L, Kuhnowski F, Berge B, Roussel M, Escoffre-Barbe M, Lafon I, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2018;**132**(24):2555–63.