Title: 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

Short title: Outcomes of deferred ASCT in myeloma PADIMAC trial

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Current Phase III trials demonstrate the benefit of upfront 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 show that high risk patients gain most survival benefit from upfront 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 median PFS of 17.0 months (95% CI: 10·5–23·2) for the sixty-three patients who achieved ≥VGPR post induction and stopped treatment until disease progression (8). MRD positive patients at day 100 had 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 ≥VGPR to 1st 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) (*Supplementary Methods*) achieved ≥VGPR to induction and received no

further treatment until disease progression. After 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 3 receiving second ASCT after further relapse. Eighteen (34.6%) did not proceed to ASCT due to entry into 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 lost 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) *(Supplementary Table 1A)*. 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% (sCR 4, CR 11, VGPR 7, PR 2, SD 1, not known 9). For those not receiving salvage ASCT, ORR was 75.0% (CR 4, VGPR 6, PR 2, SD 1, PD 3, not known 2). Patients who received salvage ASCT progressed slightly earlier (median 12.1m (95% CI: 5.8-19.8) vs 16.4m (95% CI: 7.2-31.1)) but had slightly longer 2^{nd}-PFS (median 17.7m (95% CI: 15.0-25.4) vs 12.2m (95% CI: 3.9-18.6)), resulting in similar PFS2 (median 40.9m (95% CI: 27.9-59.4) vs 40.6m (95% CI: 16.6-63.0)). There was weak evidence that post-relapse survival was longer for those receiving ASCT (4-year rate 57.8% (95% CI: 37.3-73.7) vs 29.4% (95% CI: 6.3-58.1)) and suggestion towards longer OS (4-year rate 73.3% (95% CI: 54.9-85.1) vs 59.2% (95% CI: 32.7-78.2)) *(Figure 1)*.

Salvage ASCT patients were younger (median 52.5 vs 60.5 years, p=0.01); however, no difference in gender, performance status, ISS stage, r-ISS stage, isotype, cytogenetic risk, or MRD status at PBSCH or D100 *(Table 1)* was observed. Time-to-next-treatment from 1^{st} line

was similar for receiving salvage ASCT or not (median 17.9m (95% CI: 9.7-25.0) vs 22.0m (95% CI: 13.3-34.5)) *(Supplementary Figure 1)*. 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 *(Supplementary Table 1B)*.

We report long-term outcomes of patients who achieved ≥VGPR to induction and deferred ASCT. All patients accessed treatment at first relapse however only two-thirds (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 2nd-PFS, 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 is missing.

The EMN02 trial reported 63% patients proceeding to ASCT after deferral(9). 75-month survival estimate was 69% in upfront vs 63% deferred (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 was disease refractoriness. At median 93-month follow-up, similar 8-year OS of 62.2% in upfront

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 ≥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 upfront 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

WYC: nothing to disclose; NC: grants from Blood Cancer UK, grants and other from Janssen, during the conduct of 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; RP, JC, GC, MS, SS, MK, JC, MQ, SDS, AV, CC, GP, MC, TCM, NR performed

the research; WYC, NC, RP and KY wrote the manuscript; all authors reviewed and approved the manuscript.

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Table 1 – 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%)

*34 had ASCT post-relapse, 18 no ASCT post-relapse, and 11 excluded from ASCT vs. no ASCT analyses (7 had not relapsed, 3 had relapsed but not started salvage, 1 patient had off-trial ASCT prior to relapse.)

ISS *International Staging System*, R-ISS *Revised International Staging System*, MRD *Minimal Residual Disease*, PBSCH *Peripheral Blood Stem Cell Harvest*