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ORIGINAL PAPER

Polyclonal immunoglobulin recovery in patients with newly diagnosed myeloma receiving maintenance therapy after autologous haematopoietic stem cell transplantation with either carfilzomib, lenalidomide and dexamethasone or lenalidomide alone: Subanalysis of the randomized phase 3 ATLAS trial

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Summary

Previous studies suggest that postautologous stem cell transplant (ASCT) recovery of polyclonal immunoglobulin from immunoparesis in patients with multiple myeloma is a positive prognostic marker. We performed a longitudinal analysis of polyclonal immunoglobulin concentrations and unique B-cell sequences in patients enrolled in the phase 3 ATLAS trial that randomized 180 subjects to either carfilzomib, lenalidomide, dexamethasone (KRd) or lenalidomide (R) maintenance. In the KRd arm, standard-risk patients with minimal residual disease negativity after six cycles de-escalated to R alone after cycle 8. One year from the initiation of maintenance at least partial recovery of polyclonal immunoglobulin was observed in more patients on the R arm (58/66, $p < 0.001$) and in those who de-escalated from KRd to R (27/38, $p < 0.001$) compared to the KRd arm (9/36). In patients who switched from KRd to R,

the concentrations of uninvolved immunoglobulin and the number of B-cell unique sequences increased over time, approaching values observed in the R arm. There were no differences in progression-free survival between the patients with at least partial immunoglobulin recovery and the remaining population. Our analysis indicates that patients receiving continuous therapy after ASCT experience prolonged immunoparesis, limiting prognostic significance of polyclonal immunoglobulin recovery in this setting.

KEYWORDS
ATLAS, carfilzomib, immunoparesis, lenalidomide, maintenance, myeloma

INTRODUCTION

Suppression of polyclonal (uninvolved) immunoglobulin production (immunoparesis) is a hallmark of multiple myeloma (MM) and its precursor states.[1,2] Defined as a decrease in concentration below lowest limit of normal (LLN) of at least one uninvolved immunoglobulin, immunoparesis is present in up to 90% of patients with newly diagnosed MM or relapsed/refractory disease.[3–6] In MM requiring treatment,[7] immunoparesis is associated with advanced International Staging System scores and high bone marrow infiltration by malignant plasma cells, reflecting that tumour burden may be one of the most important factors accountable for this phenomenon.[8] This may explain why the presence of immunoparesis at diagnosis or relapse has been associated with worse outcomes.[3,4,6] Multiple mechanisms responsible for the suppression of polyclonal immunoglobulin have been proposed, including decreasing the number of B-cell progenitors,[9] and suppression of proliferation and differentiation of normal B cells caused by cross-signalling between myeloma cells and marrow microenvironment leading to decrease in stimulatory cytokines such as interleukin-4 or B-cell stimulatory factor 1 and increase in inhibitory signalling activity mediated by transforming growth factor β1 or B-cell growth inhibitory factor 1.[10,11] In line with these theories, effective treatment of MM is associated with recovery of polyclonal immunoglobulin and restoration of cytokine homoeostasis.[9,12]

Based on this rationale, several studies investigated prognostic significance of uninvolved immunoglobulin recovery. It has been shown that polyclonal immunoglobulin recovery after induction therapy is associated with superior progression-free survival (PFS) and overall survival (OS) in newly diagnosed, transplant ineligible patients.[5] For patients undergoing autologous haematopoietic stem cell transplantation (ASCT), recovery from immunoparesis 1 year later was associated with superior PFS and OS.[13–16]

However, these studies were not conducted in the era of continuous and/or extended maintenance therapy, which is now common for many patients with MM. This is particularly important in the context of maintenance therapy after ASCT, where continuous single agent lenalidomide is a well-established standard of care, with multiple lines of evidence showing its survival benefit over placebo.[17–20] Recently, two studies investigating carfilzomib-based maintenance regimens demonstrated superior PFS compared to lenalidomide alone, suggesting a potential role for even more intensive maintenance therapy following ASCT.[21,22] Considering the impact that extended treatment may have not only on malignant plasma cells but also on normal plasma cells,[23,24] we evaluated polyclonal immunoglobulin recovery after ASCT and its prognostic significance in the setting of extended post-transplant maintenance therapy. Towards this goal we have performed a subanalysis of the prospective, randomized, phase 3 ATLAS trial where patients with MM after ASCT were continuously treated either with single agent lenalidomide (R) or minimal residual disease (MRD)-directed, risk-adapted therapy with carfilzomib, lenalidomide and dexamethasone (KRd).

METHODS

Patients and study design

ATLAS (NCT02659293) is an ongoing, open-label, randomized, phase 3 trial evaluating post-ASCT treatment with R alone versus KRd. The study, its protocol and amendments were approved by the institutional review board or ethics committee at each participating institution and the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland. The study is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines.

The detailed design of the ATLAS trial has been previously described.[21] Briefly, patients with MM that completed any induction therapy followed by single ASCT were eligible for enrolment up to 100 days after the ASCT. Only patients with complete data on immunoglobulin concentration (IgG, IgM and IgA) were included in this subanalysis (Tables S1 and S2).

All survival analyses were conducted using the previously published results from the unplanned interim report.[21]

Treatment

Details of treatment have been previously described.[21] Patients were randomized in a 1:1 ratio to either R or KRd.

Randomization was stratified by cytogenetic risk (high vs. standard), response after ASCT (at least very good partial response vs. less than very good partial response) and country of enrolment (Poland vs. the United States). Patients in the KRd group received treatment in 28-day cycles (carfilzomib in cycle 1 days 1 and 2 at 20 mg/m^2 and in subsequent days and cycles 36 mg/m^2 administered on days 1, 2, 8, 9, 15 and 16 of cycles 1–4 and days 1, 2, 15 and 16 from cycles 5 and beyond; lenalidomide 25 mg on days 1–21; and dexamethasone 20 mg on days 1, 8, 15 and 22). Patients in the KRd arm who had no detectable MRD as defined by the International Myeloma Working Group (at least 10^{-5} sensitivity and at least in a complete response)[25] after cycle 6 (C6), and had no high-risk cytogenetic features as defined in the protocol (no del13, t(4;14), t(14;16), del17p, or hypodiploidy) de-escalated to single agent lenalidomide (at best-tolerated dose, up to 15 mg) starting with cycle 9. Patients in the R maintenance group received single agent lenalidomide at 10 mg for the first three cycles and then at best-tolerated dose ≤15 mg for 28 days in 28-day cycles. After 36 cycles of treatment, patients in both arms received or continued to receive R maintenance. Treatment continued until disease progression, unacceptable toxicity or patient's decision.

Infection prophylaxis, per protocol, required valacyclovir 500 mg orally, once per day (or equivalent). Additional prophylaxis was at the treating investigators' discretion.

Immunoglobulin concentration measurements

Immunoglobulin concentration was measured at the beginning of each cycle by nephelometry in local laboratories at each participating site. In this study results at screening, after C6, cycle 12 (C12), cycle 18 (C18), cycle 24 (C24), cycle 30 (C30) and cycle 36 (C36) were analysed. For the purpose of this analysis, immunoparesis was defined as a decrease in at least one uninvolved immunoglobulin of more than 25% below LLN, as defined by local laboratories. We defined complete polyclonal immunoglobulin recovery as normalization of all uninvolved immunoglobulin. Partial polyclonal immunoglobulin recovery was defined as normalization of at least one uninvolved immunoglobulin. Quantitative immunoparesis was assessed as in Chakraborty et al.[4] The method is based on calculation of relative difference by subtracting LLN for each polyclonal immunoglobulin from their measured concentration and then dividing the result by the LLN. Average relative difference (ARD) was calculated for each patient as a mean of all relative differences.

$$\text{Relative difference (RD)} = \frac{\text{Immunoglobulin concentration} - \text{LLN}}{\text{LLN}}$$

$$\text{Average relative difference (ARD)} = \frac{\text{RD}_{\text{uninvolved\_IgA}} + \text{RD}_{\text{uninvolved\_IgG}} + \text{RD}_{\text{uninvolved\_IgM}}}{}$$

B-cell diversity assessment

Total number of unique sequences in immunoglobulin genes (IgH, IgK and IgL) was assessed using next-generation sequencing-based ClonoSEQ assay (Adaptive Biotechnologies) for MRD evaluation. Bone marrow samples were collected from evaluable patients (with trackable sequence identified) at screening, after C6, C12, C18, C24 and C36.

Statistical analysis

Descriptive statistics (median, 95% CI) were employed to describe the ARD and the numbers of unique sequences at the assessed timepoints. Mixed-effects model with repeated measures was used to examine the differences between the arms, with the treatment group and time of measurement as the fixed effects. For single-measurement comparisons, differences between categorical variables were calculated using Fisher's exact test and Mann–Whitney *U* test was used to compare continuous variables that did not follow normal distribution. The Kaplan–Meier method was utilized to calculate PFS and OS rates from the landmark timepoint (after C12), and the log-rank test was performed to compare the groups. The analysis was conducted using GraphPad Prism version 10.1.

RESULTS

A total of 180 patients were randomized to either KRd ($n = 93$) or R ($n = 87$). At the 31 December 2021 data cut-off, median follow-up was 33.8 months (interquartile range: 20.9–42.9). Complete data regarding immunoglobulin concentrations at screening were available for 175 (97.2%) patients, 89 (95.7%) from the KRd arm and 86 (98.9%) from the R arm. Before initiation of maintenance therapy, immunoparesis was present in 122 (69.7%) subjects—62 (69.7%) in the KRd and 60 (69.0%) in the R arm. There were no significant differences in baseline characteristics of the patients with or without immunoparesis assessed at screening (Table 1).

To describe the kinetics of polyclonal immunoglobulin recovery in the context of continuous treatment we evaluated their concentrations at subsequent timepoints. After C6, complete recovery was observed in 10/159 (6.3%) evaluable patients across both treatment arms. This proportion remained relatively low throughout the follow-up period, reaching 8/140 (5.7%), 13/122 (10.7%), 10/106 (9.4%), 11/92 (12.0%) and 10/64 (15.6%) after C12, C18, C24, C30 and C36 respectively (Figure 1; Figure S1). This low rate of complete recovery was mostly related to the prolonged suppression of uninvolved IgM, whereas the uninvolved IgA and IgG showed tendency to return to normal range with longer observation time (Figure S2). Rates of partial recovery were

TABLE 1 Baseline characteristics.

	Immunoparesis at screening ($n=122$)	No immunoparesis at screening ($n=53$)	p Value
Median age (IQR), years	59.0 (49.0–63.0)	55.0 (47.0–61.5)	0.07
Study arm			
KRd	62 (51%)	27 (51%)	0.99
R	60 (49%)	26 (49%)	
Type of monoclonal protein			
IgG	92 (76%)	34 (64%)	0.44
IgA	16 (13%)	11 (21%)	
IgM	3 (2%)	1 (2%)	
FLC	11 (9%)	7 (13%)	
Sex			
Female	57 (47%)	25 (47%)	0.99
Male	65 (53%)	28 (53%)	
Baseline ECOG performance status			
0	57 (47%)	19 (36%)	0.18
1	65 (53%)	34 (64%)	
ISS stage			
I	46 (38%)	19 (36%)	0.94
II	54 (44%)	25 (47%)	
III	22 (18%)	9 (17%)	
≥VGPR at enrolment	107 (88%)	49 (92%)	0.44
Cytogenetic profile			
Standard risk	96 (79%)	43 (81%)	0.71
High risk[a]	26 (21%)	10 (19%)	
Median time from ASCT, days (IQR)	96.0 (76.0–119.0)	98.0 (81.0–121.5)	0.57
Type of induction			
VTD	81 (67%)	32 (61%)	0.72
VCD	21 (17%)	10 (19%)	
Other[b]	20 (16%)	11 (20%)	

Note: Data are median (IQR) or *n* (%).

Abbreviations: ASCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response; VTD, bortezomib, thalidomide, dexamethasone.

[a]The presence of del13, t(4:14), t(14:16), del17p or hypodiploidy.

[b]Other induction regimens included KRd, Vd, VTD-PACE, PAD and VRd.

higher, having been observed in 75 (47.2%), 86 (61.4%), 79 (64.8%), 74 (69.8%), 62 (67.4%) and 37 (57.8%) patients after C6, C12, C18, C24, C30 and C36 respectively (Figure 1; Figure S1).

There were significant differences in ARD between the patients continuously treated with KRd (KRd36) and those in the R arm ($p=0.007$). Considering the study design which involved de-escalation from KRd to R after cycle 8 (C8) for a subset of MRD-negative standard-risk patients (KRd8-R), these patients were analysed separately from the KRd36 arm, following C8. Starting from the assessment at C12, the ARD was similar for patients in the R arm and the KRd8-R arm ($p=0.27$), while it was lower for the KRd36 as compared to KRD8-R ($p<0.001$). The median ARD at screening for patients in the KRd and R arms equals −21% (95% CI: −32% to −8%) and −19% (−33% to −6%) respectively. After C6, however, ARD was lower (more deviated from normal) in the KRd am, −39% (−47% to −28%) vs. 0% (−8% to +26%). The ARD at C12 for patients in the KRd8-R group equalled −3% (−30% to +27%), in the KRd36 group −47% (−57% to −27%) and in the control R arm +24% (+6% to +45%) (Figure 2A). At later timepoints, the ARD continued to increase in patients treated with lenalidomide and remained at the same, low level for those continuously treated with KRd (C18: −37% [−52% to −21%], C24: −13% [−54% to +1%], C30: −35% [−56% to 0%] and C36: −33% [−58% to +21%], Figure 2A). Starting from C18, the median ARD in the KRd8-R and R arms were as follows: +21% (+7% to +60%) vs. +50% (+19% to +65%) at C18; +37% (+8% to +62%) vs. +44% (+20% to +94%) at C24; 37% (+16% to +74%) vs. 28% (+17% to +94%) at C30;

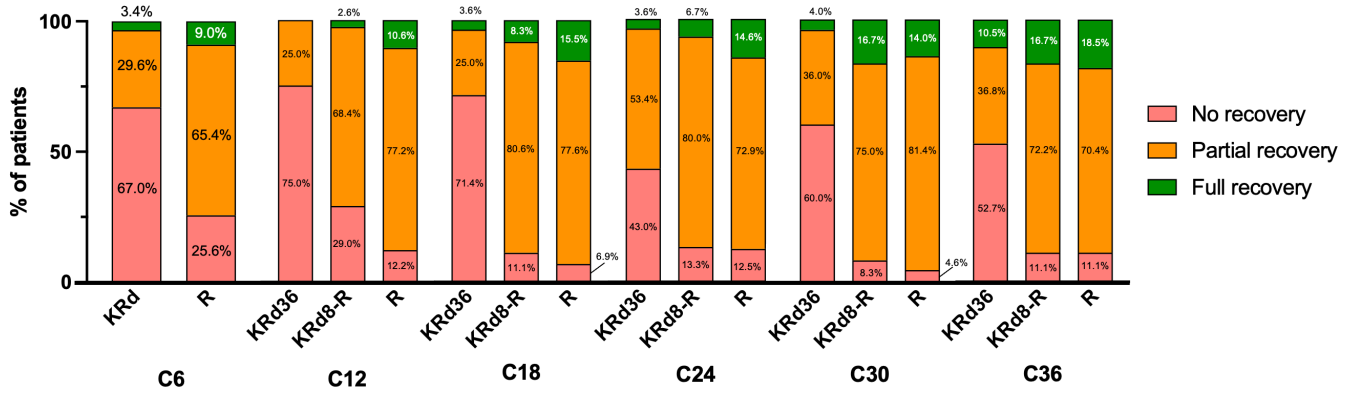

FIGURE 1 Rates of polyclonal immunoglobulin recovery at different timepoints for each study arm and separately for those patients who de-escalated the therapy from KRd to R (KRd8-R) after cycle 8.

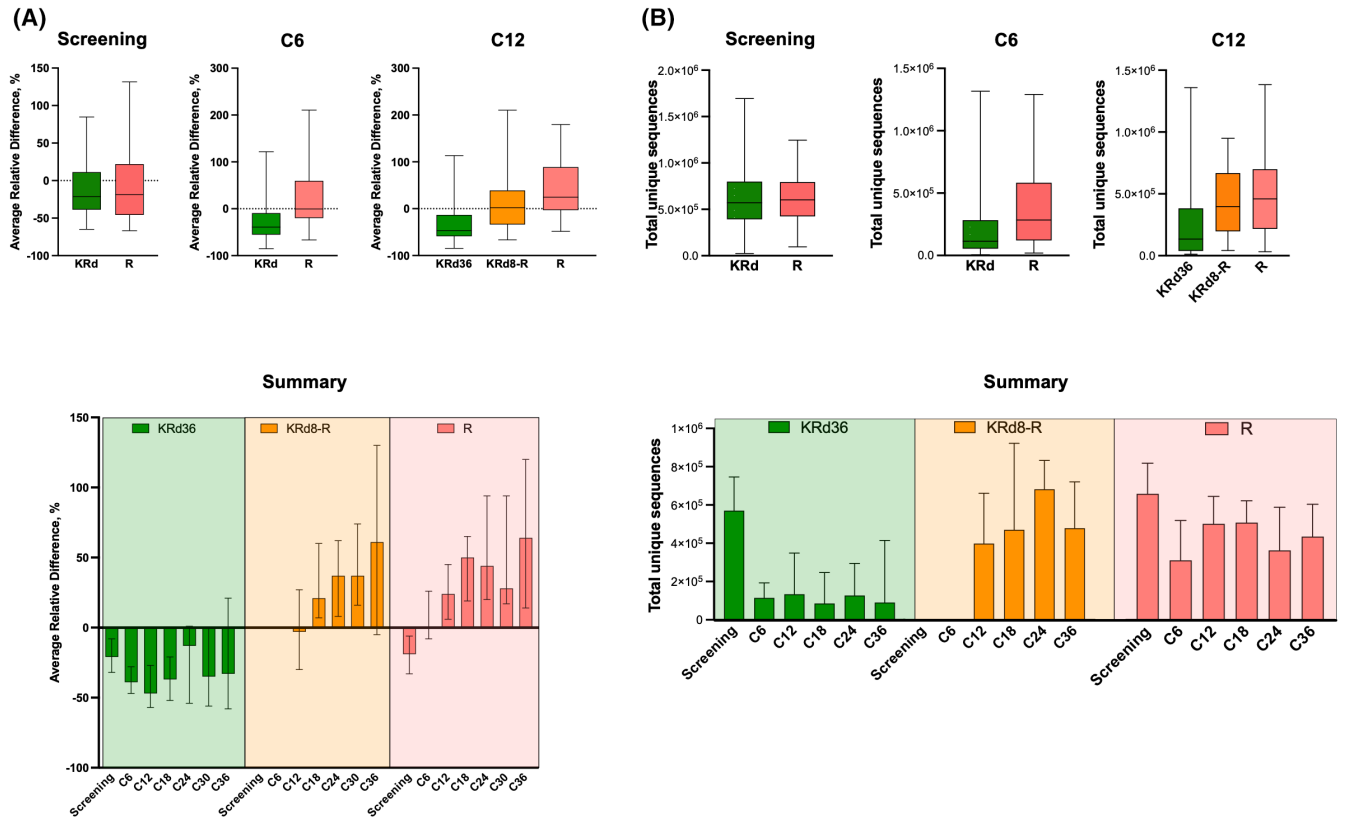

FIGURE 2 (A) Average relative difference in concentration of uninvolved immunoglobulin assessed at different timepoints. (B) Number of total unique sequences for immunoglobulin genes detected in bone marrow samples. Values are reported for each study arm and separately for the patients who de-escalated the therapy from KRd to R (KRd8-R) after cycle 8.

and +61% (−5% to +130%) vs. +64% (+14% to +120%) at C36. A similar pattern of persistent immunoparesis in patients treated continuously with KRd emerged in the qualitative analysis. After C6, partial and complete recovery of polyclonal immunoglobulin were observed in 24/81 (29.6%) and 3/81 (3.4%) of patients in the KRd arm compared with 51/78 (65.4%) and 7/78 (9.0%) in the R arm. After C12, partial and complete recovery were seen in 9/36 (25.0%) and 0/36 (0%) for KRd36, in 26/38 (68.4%) and 1/38 (2.6%) for KRd8-R and in 51/66 (77.2%) and 7/66 (10.6%) for R. The rates of partial and complete recovery of uninvolved immunoglobulin remained lower for continuous KRd arm through further timepoints (Figure 1).

Impact of continuous treatment on B cells was further assessed by measuring the number of unique immunoglobulin gene sequences. The results were congruent with quantitative polyclonal immunoglobulin assessment (Figure 2B). The differences were significant for the comparison between KRd36 versus R ($p = 0.013$), and KRd36 versus KRd8-R ($p = 0.003$), whereas non-significant between R versus KRd8-R, starting

at C12 ($p = 0.46$). At screening, the median number of total unique sequences among evaluable ($n = 48$) patients randomized to the KRd arm equalled 570 552 (95% CI: 463 912–745 763) and 601 994 (95% CI: 509 802–747 969) in the R arm ($n = 44$). After C6, patients treated with KRd ($n = 53$) had less diverse B-cell repertoire than those on R ($n = 44$) (114 519; 95% CI: 71 776–190 698 vs. 284 350; 95% CI: 167 952–474 260). Interestingly, patients who de-escalated therapy to R after C8 ($n = 22$) expanded their number of unique B cells to the level observed in the R arm ($n = 41$) (397 239; 95% CI: 215 414–611 114 vs. 458 864; 95% CI: 281 425–574 432) while the total numbers of unique sequences among patients continuously treated with KRd remained lower (134 058; 95% CI: 54 881–348 425, $n = 23$).

To examine the correlation between the suppression of polyclonal immunoglobulin production and response to treatment, we analysed the ARDs in subgroups of MRD-negative and MRD-positive patients, based on previously reported results for MRD status after C6.[21] At this timepoint, median ARD was significantly lower in MRD-negative patients (–26% [–33% to –14%] vs. –9% [–19% to +6%], $p = 0.027$). Intriguingly, this difference was partially related to the MRD-negative patients treated on the R arm (Figure 3A). We did not observe any significant differences in total unique sequences number based on MRD status (Figure 3B).

Next, we assessed if complete polyclonal immunoglobulin recovery after C12 is associated with favourable outcomes. Notwithstanding that patients with early progression were excluded from this analysis, recovery of polyclonal immunoglobulin at C12 was not associated with significant differences in PFS (median 25.2 months for recovered vs. 47.1 months for not recovered, HR = 2.41 [0.62–9.47], $p = 0.21$; Figure 4A) or OS (median 49.8 for recovered vs. not reached for not recovered, HR = 1.16 [0.13–10.65], $p = 0.90$; Figure 4B). In addition, at least partial recovery of polyclonal immunoglobulin at C12 was not significantly associated with PFS (median 53.4 months for recovered vs. 47.1 months for not recovered, HR = 1.07 [0.54–2.10], $p = 0.85$; Figure 4C) or OS (median not reached for recovered vs. not reached for not recovered, HR = 1.22 [0.34–4.37], $p = 0.76$; Figure 4D). When adjusted for the treatment arm (KRd36, KRd8-R, R) partial polyclonal immunoglobulin recovery also did not predict superior PFS (Figure 5). From the perspective of the current standard of care consisting mainly of R maintenance, we analysed landmark PFS and OS after C12 for subjects on the R and KRd8-R arms; there was again no prognostic significance of complete or partial uninvolved immunoglobulin recovery (Figure S3). Also, the number of unique B-cell sequences at C12 and the presence of premaintenance immunoparesis were not associated with PFS (data not shown).

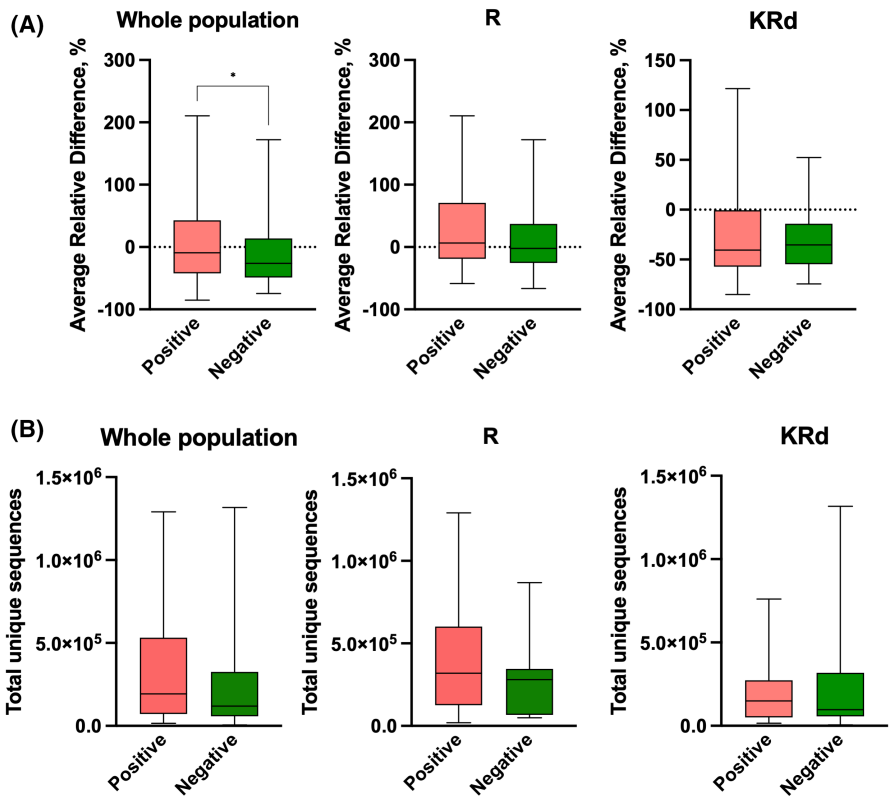

FIGURE 3 (A) Average relative difference in uninvolved immunoglobulin concentration and (B) total number of unique sequences for immunoglobulin genes measured after C6 in minimal residual disease (MRD)-negative and MRD-positive patients, MRD was assessed at the corresponding timepoint. Results are presented for the whole population and separately for the two study arms. Statistically significant differences ($p < 0.05$) are marked with '*'.

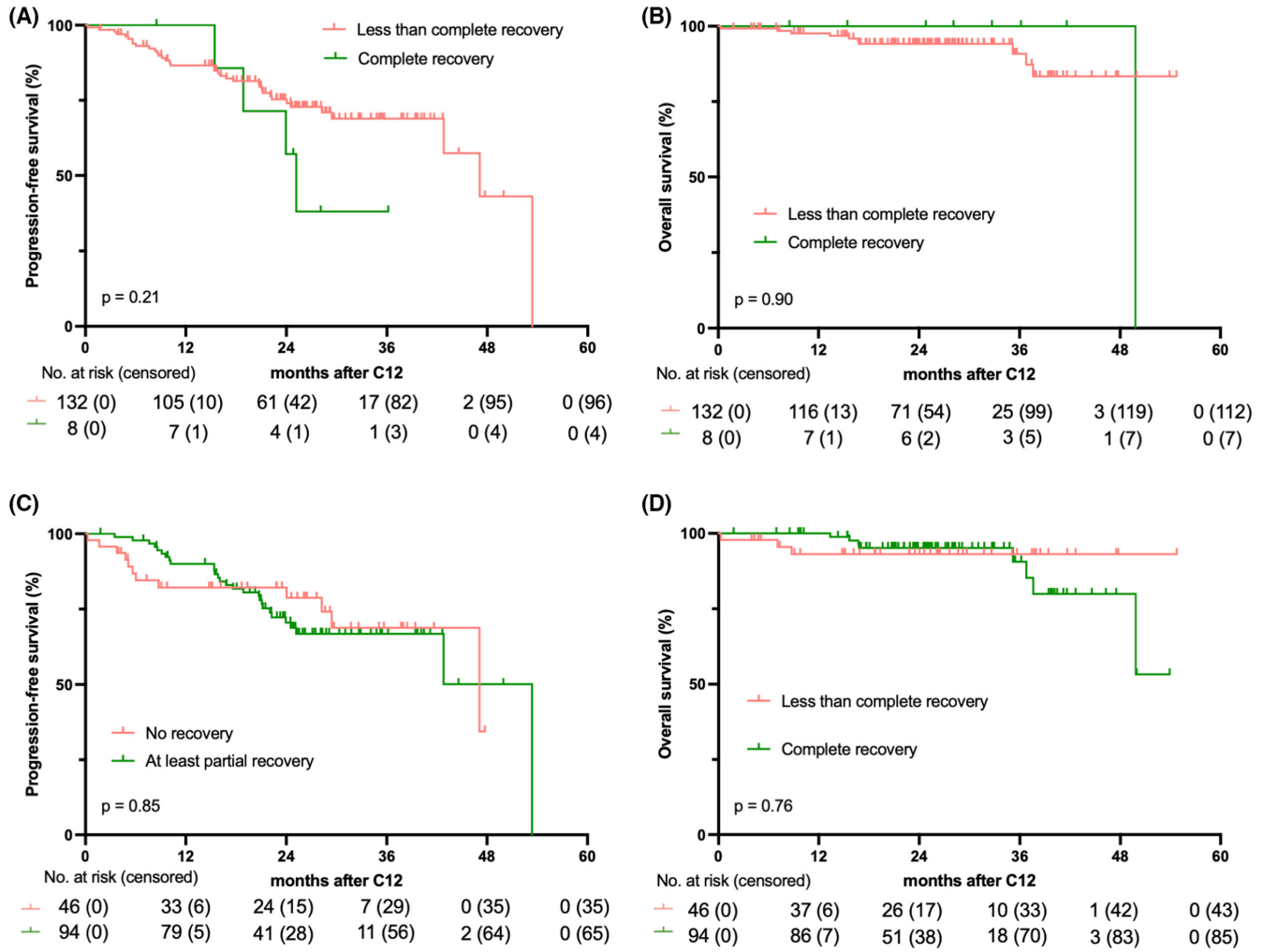

FIGURE 4 Landmark (after C12) progression-free survival (PFS) and overall survival (OS) rates comparison in subgroups of patients with complete, partial or without any recovery of uninvolved polyclonal immunoglobulin. (A) PFS assessed in complete versus less than complete recovery. (B) OS assessed in complete versus less than complete recovery. (C) PFS assessed in group without any recovery versus at least partial recovery. (D) OS assessed in group without any recovery versus at least partial recovery.

DISCUSSION

This is, to our knowledge, the first published report indicating no positive association of polyclonal immunoglobulin recovery with survival in patients after ASCT in a population uniformly treated with lenalidomide-based maintenance, using either single agent lenalidomide or KRd. The results of this post-hoc analysis from a prospective evaluation of patient data from a randomized phase 3 trial indicate that the prognostic role of polyclonal immunoglobulin recovery is limited in patients receiving continuous single agent or combination therapy in the post-transplant setting.

To date, four studies evaluated the impact of immunoparesis after ASCT in MM.[13–16] All of them were retrospective in nature and included 50, 108, 197 and 295 patients respectively. In three of these four trials, uninvolved immunoglobulin recovery 1 year after ASCT was associated with improved PFS and OS and in one trial it was associated with improved OS. In only one of these studies a significant proportion (112/197 [57%]) of patients were treated with lenalidomide maintenance.[14] Other reports assessed patients without any maintenance therapy[16] or with therapies that are no longer in use in the post-transplant setting, such as thalidomide[13] or interferon-α.[15] To make our analyses comparable, we used here the same definitions of immunoparesis (25% below LLN) and polyclonal immunoglobulin recovery as in these publications.

In our analysis, only 5.7% of patients experienced complete recovery of all uninvolved immunoglobulin after 12 cycles of therapy. It is strikingly low when compared to previous studies that reported rates of 52%, 18.6% and 34.2%. Noteworthy, the lowest rate was reported by Jimenez-Zepeda et al.,[14] possibly reflecting the 'plasmacytotoxic' impact of contemporary maintenance/consolidation regimens. The low proportion of patients with completely recovered immunoglobulin in our study was consistently observed throughout the follow-up period, up to 3 years of therapy.

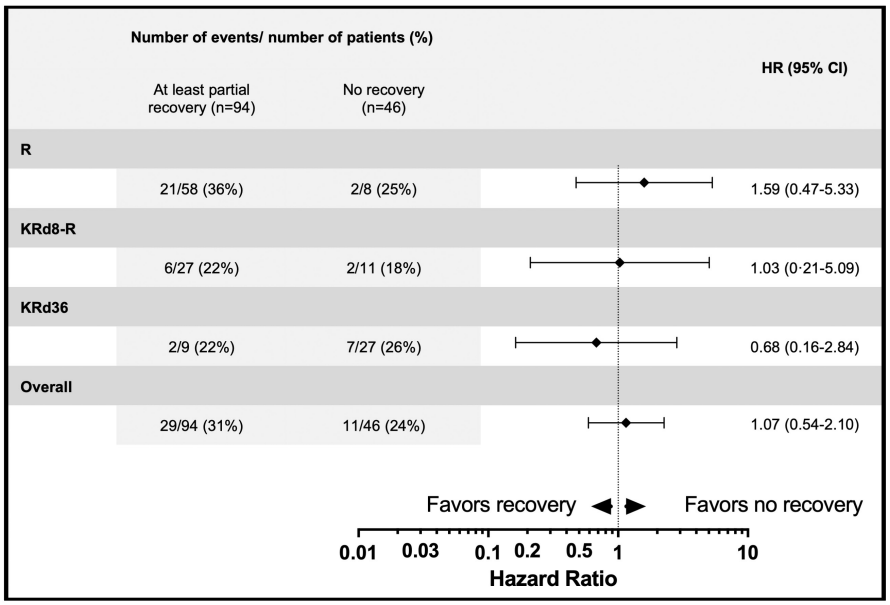

FIGURE 5 Forest plot showing impact of at least partial polyclonal immunoglobulin recovery after cycle 12 on landmark progression-free survival in different study arms.

Interestingly, this ongoing immunoparesis was mostly related to decreased concentration of uninvolved IgM. The role of this particular isotype is noteworthy, considering the results of an analysis of over 5000 patients with newly diagnosed MM which revealed that the depth of IgM suppression at diagnosis, but not IgA nor IgG, was associated with survival.

A unique aspect of this study is the ability to assess the prevalence of immunoparesis and its impact on PFS and OS in patients continuously treated with KRd, a more intensive approach than single agent maintenance. We demonstrate here that while more intensive post-ASCT treatment generated superior PFS in the unplanned interim analysis, it was associated with deeper suppression of uninvolved immunoglobulin production. This, in part, may explain the slightly higher rate of grade 3 or higher infections observed in the KRd arm (14% vs. 7%, $p = 0.12$, described in detail in Table S3), although not appearing to affect favourable PFS for this arm. The low rates of grade 3 or higher infections in this study precluded an analysis of the association between immunoglobulin recovery and infection risk; larger sample size would be needed to definitively analyse this association.

The study design involved de-escalation of therapy from KRd to R, which allowed for evaluation of the impact of proteasome inhibitor de-escalation on immunoglobulin recovery. Following discontinuation of carfilzomib, the levels of polyclonal immunoglobulin approached the levels observed in patients treated with lenalidomide from the beginning of post-ASCT treatment. This was even more evident for the number of unique B-cell sequences; patients in the KRd8-R group reached the B-cell diversity level of those in the continuous R arm just 4 months after de-escalating therapy. In the original trial report[21] the patients who de-escalated therapy still experienced the benefit of initial KRd treatment and their outcomes appeared better than standard-risk, MRD-negative patients from the R arm. Based on this observation, it is possible that the lack of polyclonal immunoglobulin recovery in the context of continuous treatment is more of a proxy for 'plasmacytotoxic' drug activity than a reflection of immune reconstitution needed for appropriate disease control. The observation that MRD-negative patients showed lower ARD adds another argument for this reasoning. Moreover, recently presented results from the PETHEMA/GEM group also did not confirm the prognostic significance of immunoglobulin recovery while on maintenance therapy with lenalidomide, dexamethasone and ±ixazomib.[26]

We anticipate that achieving immune recovery might ultimately be desired for treatment outcome to lower the risk of infections and/or enhance tumour immune surveillance. At this interim analysis, we do not have sufficiently long follow-up to assess whether immunoglobulin recovery at later timepoints could affect PFS, OS or rates of infections. Nevertheless, the results of the KRd8-R subgroup appear to indicate that the adverse impact of initial post-ASCT KRd treatment on humoral immunity can be rapidly reversed through treatment de-escalation, guided by MRD and risk status, while still retaining the clinical benefits of the initial intensive therapy. We anticipate that results from the ongoing MRD2STOP study (NCT04108624), in which patients who achieve sustained MRD negativity at 10^{-6} sensitivity level combined with undetectable M-spike and no evidence of disease by positron emission tomography can discontinue maintenance treatment will further help to unravel the effect of not only de-escalation but also a cessation of lenalidomide maintenance on humoral

immunity. It will be particularly interesting in the context of recently published results documenting humoral immune reconstitution in patients who discontinued quadruplet, carfilzomib-containing therapy after achieving MRD negativity,[27] with our data suggesting that this effect may be mostly driven by the discontinuation of the proteasome inhibitor.

This study has several limitations. The analysis was not preplanned and included post-hoc assessment of laboratory measurements collected during a randomized, phase 3 clinical trial. While nephelometry techniques were similar across institutions, there may be slight differences in measured immunoglobulin levels across sites. We arbitrarily chose timepoints for analysis to allow for comparison with previous studies. While similar to previous reports, this study population, once divided by treatment arms, is relatively low. Polyclonal immunoglobulin and B-cell diversity recovery may reflect the state of B-cell function recovery, however, at the time of analysis, it is not clear if they are associated with lower risk of infection or enhanced disease control. In the case of the number of unique B-cell sequences, there is no known 'normal' number that would indicate a normal functioning immune system.

The results of our study do not support a prognostic role of polyclonal immunoglobulin recovery at 1 year after ASCT in the contemporary landscape of lenalidomide-based single agent and combination maintenance therapies. Combining large prospective datasets with paired immunoglobulin and B-cell repertoire data will be key to further understanding the implications of immunoparesis and B-cell diversity in the myeloma therapy continuum.

AUTHOR CONTRIBUTIONS

Tadeusz Kubicki, Dominik Dytfeld, Benjamin A. Derman and Andrzej J. Jakubowiak conceptualized and designed the study, were responsible for data analysis and drafted the manuscript. Tadeusz Kubicki visualized the data. All authors were responsible for locally conducting the study, and data collection; edited, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

TK reports honoraria from AbbVie and Celgene (Bristol Myers Squibb) and financial support for attending meetings or travel support (or both) from Sanofi. DD reports speaker honoraria and participation in advisory boards for Amgen and Celgene (Bristol Myers Squibb) and had conference fees paid by Amgen. TW reports honoraria from AbbVie, Amgen, BeiGene, Celgene (Bristol Myers Squibb), Gilead, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Roche and Takeda; conference fees or travel support (or both) from AbbVie, Amgen, Celgene (Bristol Myers Squibb), Gilead, GlaxoSmithKline, Janssen-Cilag, Pfizer, Roche and Takeda; and advisory board participation for AbbVie, Amgen, BeiGene, Celgene (Bristol Myers Squibb), Gilead, GlaxoSmithKline, Janssen-Cilag, Pfizer, Roche, Novartis and Takeda. KJ reports grants paid to his institution and payment for expert testimony from Janssen; honoraria from Amgen, Celgene (Bristol Myers Squibb), GlaxoSmithKline, Janssen, Sandoz and Takeda; financial support for attending meetings or travel support (or both) from Amgen, Celgene and Janssen; and consulting and advisory board participation for Amgen, Celgene (Bristol Myers Squibb), Janssen, Sandoz and Takeda. AD-S reports honoraria for presentations and lectures from Amgen and Celgene (Bristol Myers Squibb); and financial support for attending meetings or travel support (or both) and advisory board participation from Celgene (Bristol Myers Squibb). KG reports honoraria from Amgen and Celgene (Bristol Myers Squibb). BP reports grants or contracts from AbbVie, Amgen, Celgene (Bristol Myers Squibb) and Janssen; consultation fees from AbbVie, Roche and Sandoz; honoraria for lectures and presentations from AbbVie, Amgen, Celgene (Bristol Myers Squibb) and Janssen; and financial support for attending meetings or travel support (or both) from AbbVie and Celgene (Bristol Myers Squibb). JR reports speaker honoraria and advisory board participation from Amgen, Celgene (Bristol Myers Squibb) and Janssen. LU-Z reports financial support for attending meetings or travel support (or both) from Janssen. DM reports lecture and presentation fees from Amgen and Janssen. OBL reports participation on an advisory board for MorphoSys. BAD reports consulting fees from COTA Healthcare, Janssen and Sanofi; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from MJH Life Sciences and Plexus Communications. AJJ reports consulting fees and honoraria for lectures and presentations from AbbVie, Amgen, Celgene (Bristol Myers Squibb), Gracell, GlaxoSmithKline, Janssen and Sanofi-Aventis. All other authors declare no competing interests.

CLINICAL TRIAL REGISTRATION

ATLAS is registered with ClinicalTrials.gov, NCT02659293 and EudraCT, 2015-002380-42.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

The study, its protocol and amendments were approved by the institutional review board or ethics committee at each participating institution and the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland.

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The ATLAS trial was funded by Amgen and Celgene (Bristol Myers Squibb).

PATIENT CONSENT STATEMENT

Informed consent was collected from patients involved in this study, in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines.

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SUPPORTING INFORMATION

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

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