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Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, and Dexamethasone as Induction and Extended Consolidation Improves Outcome in Ultra-High-Risk Multiple Myeloma

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ABSTRACT

PURPOSE The multicenter OPTIMUM (MUKnine) phase II trial investigated daratumumab, low-dose cyclophosphamide, lenalidomide, bortezomib, and dexamethasone (Dara-CVRd) before and after autologous stem-cell transplant (ASCT) in newly diagnosed patients with molecularly defined ultra–high-risk (UHiR) multiple myeloma (NDMM) or plasma cell leukemia (PCL). To provide clinical context, progression-free survival (PFS) and overall survival (OS) were referenced to contemporaneous outcomes seen in patients with UHiR NDMM treated in the recent Myeloma XI (MyeXI) trial.

METHODS Transplant-eligible all-comers NDMM patients were profiled for UHiR disease, defined by presence of ≥2 genetic risk markers t(4;14)/t(14;16)/t(14;20), del(1p), gain(1q), and del(17p), and/or SKY92 gene expression risk signature. Patients with UHiR MM/PCL were offered treatment with Dara-CVRd induction, V-augmented ASCT, extended Dara-VR(d) consolidation, and Dara-R maintenance. UHiR patients treated in MyeXI with carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide, or lenalidomide, dexamethasone, and cyclophosphamide, ASCT, and R maintenance or observation were identified by mirrored molecular screening. OPTIMUM PFS at 18 months (PFS18m) was compared against MyeXI using a Bayesian framework, and patients were followed up to the end of consolidation for PFS and OS.

RESULTS Of 412 screened NDMM OPTIMUM patients, 103 were identified as UHiR or PCL and subsequently treated on trial with Dara-CVRd; 117 MyeXI patients identified as UHiR formed the external comparator arm, with comparable clinical and molecular characteristics to OPTIMUM. Comparison of PFS18m per Bayesian framework resulted in a 99.5% chance of OPTIMUM being superior to MyeXI. At 30 months' follow-up, PFS was 77% for OPTIMUM versus 39.8% for MyeXI, and OS 83.5% versus 73.5%, respectively. Extended post-ASCT Dara-VRd consolidation therapy was highly deliverable, with limited toxicity.

CONCLUSION Our results suggest that Dara-CVRd induction and extended post-ASCT Dara-VRd consolidation markedly improve PFS for UHiR NDMM patients over conventional management, supporting further evaluation of this strategy.

ACCOMPANYING CONTENT

Data Supplement
Protocol

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INTRODUCTION

The prognosis for patients with newly diagnosed multiple myeloma (NDMM) has significantly improved over the past 20 years, with more than half of younger patients now surviving for over 10 years.[1,2] However, around 25% of patients still relapse within 2 years of initiation of therapy, even if treated with proteasome inhibitor/lenalidomide (PI/immunomodulatory drug [IMiD]) combination induction therapy, high-dose melphalan with autologous stem-cell transplant (ASCT), and lenalidomide (Len) maintenance, which is the current standard-of-care (SOC) treatment for fit NDMM in many health care systems.[3-5] For such patients, there is currently no consensus best

CONTEXT

Key Objective

Outcomes for patients with newly diagnosed ultra-high-risk (UHiR) multiple myeloma (MM) or plasma cell leukemia (PCL) remain unsatisfactory. As salvage of UHiR MM and PCL at relapse is challenging, identifying patients with UHiR disease upfront and optimizing their first-line therapy appears a promising strategy. This trial investigated intensified induction and extended consolidation post-autologous stem-cell transplantation (ASCT) with daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone (Dara-CVRd) for UHiR MM or PCL identified through central molecular screening of all-comers newly diagnosed multiple myeloma (NDMM) patients.

Knowledge Generated

Molecular screening for UHiR MM at diagnosis was highly deliverable and led to consistent identification of patients with UHiR MM and PCL. Their progression-free survival was markedly improved with intensified induction and post-ASCT consolidation over contemporaneous conventional management, contextualized through outcomes of patients with UHiR MM from the Myeloma XI trial. The results suggest a specifically important role for extended consolidation in preventing early post-ASCT relapse.

Relevance *(S. Lentzsch)*

OPTIMUM is the first trial specific for UHiR NDMM and PCL, with a median progression free-survival yet to reach after more than 3 years of follow-up. The results show that Dara-CVRd induction, ASCT, and extended Dara-VR(d) consolidation is a very effective therapy in UHiR/PCL MM patients. The concept should be further investigated in phase III clinical trials to establish a standard of care for UHiR NDMM and PCL patients.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

treatment standard. Patients derive less benefit from relapse therapy, and have shorter overall survival (OS), suggesting rapid evolution of resistance to therapy and increasing proliferation with relapse.[6,7] Accordingly, patients with ultra-high-risk (UHiR) MM are in urgent need of early, upfront identification and improved, tailored first-line treatment approaches to induce and maintain disease control.

Established molecular markers predictive of UHiR NDMM include (1) the co-occurrence of two or more of the independent genetic risk markers (ie, 'double hit') canonical translocations t(4;14) or t(14;16)/t(14;20), and copy-number aberrations del(1p), gain(1q), or del(17p),[8-11] which are associated with genomic instability[12-14]; (2) gene expression profiling (GEP) signatures such as SKY92, which are independent of a double hit, and associated with tumor proliferation.[15-17] Primary plasma cell leukemia (PCL) is classically defined by >20% circulating plasmablasts (cPBL), with very recent analyses suggesting similar features for patients with cPBL between 5% and 20%, and is typically characterized by high proliferation rates and early relapse with SOC therapy, akin to UHiR MM.[18-22]

Recent retrospective exploratory analyses suggest intensifying therapy before, and in particular after, ASCT in younger, fitter patients with combination consolidation and maintenance therapy, including daratumumab, may improve patient outcome for UHiR patients.[9,23-25] However, comparative prospective evidence evaluating benefit in patients with UHiR NDMM or PCL is lacking.

The rarity of UHiR/PCL precludes randomized clinical trials.[26] Furthermore, the poor outcomes with SOC therapy make conventional trial designs ethically questionable. Recent advances in the design of prospective external control trials offer the option of providing additional clinical context over single-arm trial data, especially when focusing on stringently defined groups of patients.[27] To control for potential biases and inherent uncertainties, we compared against a recent external phase III clinical trial data set solely recruited within the same health care system, the UK National Health Service (NHS), with similar entry criteria for NDMM, and applied mirrored molecular screening for UHiR MM in both cohorts. We term this a digital comparator design herein and use this approach in the OPTIMUM (Myeloma UK nine) trial to compare intensified therapy with daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone (Dara-CVRd) induction and consolidation for UHiR MM and PCL (UHiR/PCL) against current standard therapy.

METHODS

Study Design

The OPTIMUM trial (ClinicalTrials.gov identifier: NCT03188172) is a phase II multicenter digital comparator trial investigating an intensive combination treatment schedule comprising Dara-CVRd, before and after ASCT, versus an external SOC PI/IMiD induction, ASCT, and Len maintenance

treated data set from a phase III clinical trial. This manuscript reports the planned final and further follow-up analyses after the completion of both consolidation treatment periods for all patients. The final analysis reports the primary outcome of progression-free survival at 18 months (PFS18m); further follow-up reports updated PFS, and OS after completion of consolidation 1 and 2. Secondary and safety outcomes relating to induction and consolidation 1 and 2 treatment are reported.

The trial was designed as a single-arm phase II trial with interim assessments for futility, using a Bayesian strategy for monitoring multiple outcomes[28-30] and comparison of activity against a molecularly matched external control data set from the Myeloma XI/XI+ trial (ClinicalTrials.gov identifier: NCT01554852; referred to as MyeXI herein).[4,17,31] Tumor risk profiling for MyeXI was centrally performed, using the same criteria and molecular methods, in the same laboratory as for OPTIMUM. MyeXI was a multicenter open-label phase III, randomized controlled trial comparing carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide (KCRD) versus lenalidomide, dexamethasone, and cyclophosphamide (CRD), or thalidomide, dexamethasone, and cyclophosphamide induction. Patients were enrolled between December 2013 and April 2016 across 88 UK sites.

Full details of the OPTIMUM Protocol, including study design, eligibility, treatment, study end points, and statistical methodology, have been published.[32] The trial was designed to be pragmatic in its inclusion criteria and to be inclusive as MyeXI.[31] The trial received national research ethics approval from the NHS National Research Ethics Service London, Fulham (REC Numbers: 17/LO/0022 and 17/LO/0023), the institutional review boards of the participating centers, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, United Kingdom), and was undertaken according to the Declaration of Helsinki and the principles of Good Clinical Practice. All patients provided written informed consent.

Treatment and Procedures

In OPTIMUM, patients with suspected (or confirmed) symptomatic NDMM or PCL and deemed fit to receive intensive therapy were eligible for the OPTIMUM screening protocol and were asked to provide a bone marrow sample as part of standard diagnostic investigations for central trial molecular screening at The Institute of Cancer Research (London, United Kingdom). Patients with confirmed symptomatic NDMM as per International Myeloma Working Group (IMWG) criteria[33] and UHiR disease were offered participation in the OPTIMUM treatment protocol. Patients with non-UHiR MM or declining entry into OPTIMUM treatment were included in a real-world outcome data collection protocol (Fig 1).

UHiR was established on the basis of central trial genetics (≥two high-risk lesions: t(4;14), t(14;16)/t(14;20), gain(1q), del(1p), del(17p)) using multiplex ligation-dependent probe amplification (MRC Holland, Amsterdam, the Netherlands) and quantitative reverse transcriptase polymerase chain reaction (Applied Biosystems, Waltham, MA) assays,[10,17,34-36] or presence of an MMProfiler SKY92 GEP signature (SkylineDx, Rotterdam, the Netherlands),[37-39] or patients with PCL (circulating plasmablasts >20%)[17,19,37] (Data Supplement [Supplementary Material], online only). Patients with PCL were immediately offered participation in OPTIMUM upon local laboratory diagnosis.

Up to two cycles of bridging therapy with SOC induction were allowed (at the time, most commonly bortezomib, thalidomide, and dexamethasone) while central investigations were undertaken. After informed consent to OPTIMUM, participants were given induction with Dara-CVRd to maximum response (or a maximum of six cycles of induction), ASCT, consolidation part 1 with Dara-VRd for six cycles, consolidation part 2 with Dara-VR for 12 cycles, and maintenance using Dara-R until progression. Treatment details are provided in the Data Supplement (Supplementary Figure 1).

Peripheral blood serum was collected after each cycle for central response assessment (Birmingham University, Birmingham, United Kingdom). Bone marrow aspirates were centrally analyzed for minimal residual disease (MRD) at baseline, postinduction, day 100 post-ASCT, and after consolidation 2 using a validated flow cytometry assay (Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds, United Kingdom; Data Supplement [Supplementary Material]), with 1×10^{-5} defined as cutoff for MRD negativity (MRD-).

Data are collected at each cycle of treatment and at the end of each phase of treatment, thus limiting loss to follow-up. Adverse events (AEs) were collected for all participants from the first investigational medicinal product dose until 90 days after the date of the last dose of study drugs. Participants continue to have data collected for progression and survival after cessation of trial treatment.

Outcomes

The primary end point to assess efficacy was PFS status at 18 months after registration to screening protocol (PFS18m). The primary end points for interim futility analyses were MRD status 100 days post-ASCT and PFS at 100 days post-ASCT (or equivalently 12 months for patients not proceeding to ASCT).

Secondary end points reported include PFS as a time-to-event end point (key exploratory comparison to MyeXI); safety and toxicity (as graded by Common Terminology Criteria for Adverse Events V4.0); MRD response; maximum response (as defined by IMWG criteria[33]); treatment compliance; and

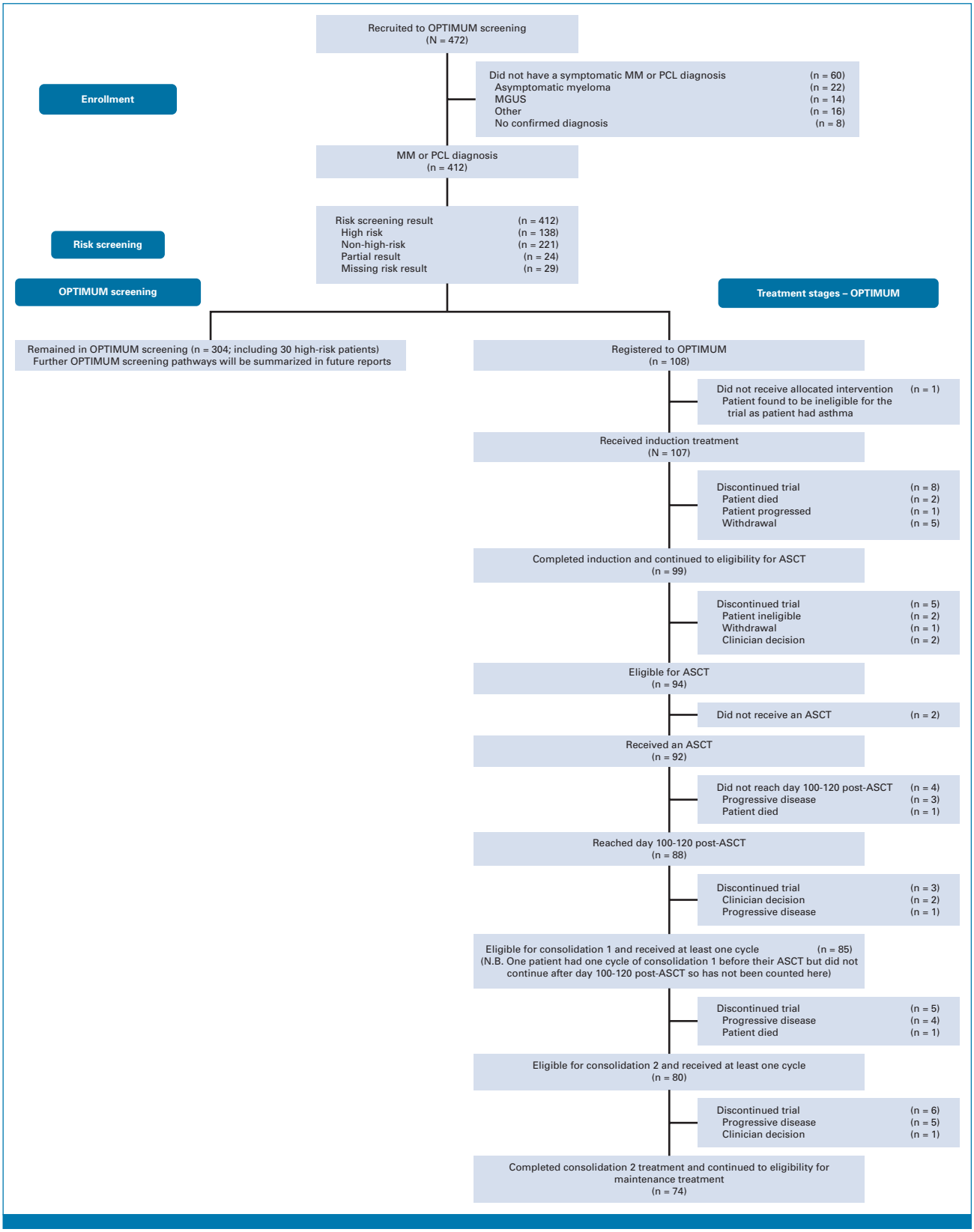

FIG 1. Participant flow diagram up in the OPTIMUM trial from registration and start of central screening to end of consolidation 2. Number of patients who discontinued trial therapy and reasons for discontinuation are provided for each therapy stage. ASCT, autologous stem-cell transplantation; MM, multiple myeloma; PCL, plasma cell leukemia.

OS. The primary end point for the OPTIMUM screening protocol, proportion of patients with molecular risk-defining investigations performed within 8 weeks, is also reported. All outcome definitions matched those of MyeXI.

Statistical Analysis

The Bayesian model for primary end point was based upon seven mutually exclusive events (accounting for interim futility end points) resulting in a Dirichlet prior (Data Supplement [Supplementary Table 1]). Interim futility assessments were specified every 10 patients using predefined stopping boundaries for halting recruitment. The OPTIMUM posterior was compared with the MyeXI digital comparator for superiority, with at least 85% probability the treatment arm would be deemed efficacious.

To enable preplanned use of the most recent outcome data from MyeXI, which was not analyzed or published at the time of trial design, the digital comparator prior was originally specified using data from Myeloma IX.[40] Potential outcomes were considered for MyeXI digital comparator with corresponding sample sizes up to 105 patients prespecified in the protocol.[32] Analysis was performed on all participants registered to OPTIMUM who received at least one dose of any trial treatment. For primary end point analysis, patients with undeterminable PFS18m were excluded from analysis. Time-to-event methodology was also applied to PFS data to include all patients. PFS curves were calculated using the Kaplan-Meier method. CIs for response and MRD status are calculated using the Clopper-Pearson method. Credible intervals from the Bayesian model were reported using highest-density intervals. Post hoc robustness analyses were performed using propensity score matching (Data Supplement [Supplementary Material]) to explore robustness to selection of the digital comparator population. All analyses were preplanned, unless specified. Statistical analysis was undertaken using SAS software, version 9.4.

RESULTS

Patient Flow and Genetic Testing

Between September 2017 and July 2019, 472 patients entered the OPTIMUM screening protocol, 412 of whom were confirmed to have symptomatic MM or PCL and underwent molecular screening (Fig 1). Genetic risk status was successfully determined for both genetic and GEP in 359 patients (87%), and partial results for genetic or GEP for 24 patients (6%). In 29 patients (7%), no result could be obtained, primarily because of poor bone marrow aspirate quality. Median time for patients to receive a risk status result was 18 days (IQR, 13-22; range, 0-37 days), well within the protocol-defined maximum limit of 8 weeks, equivalent of two cycles of bridging therapy, meeting the

TABLE 1. Baseline Characteristics of UHiR/Plasma Cell Leukemia Patients in the MyeXI Comparator and OPTIMUM Trial

	MyeXI		OPTIMUM
Characteristic	N = 120	n = 98[a]	N = 107
Age at registration/random assignment, years			
Median (range)	62 (33-69)		60 (35-78)
Sex, No. (%)			
Male	69 (57.5)		64 (59.8)
Female	51 (42.5)		43 (40.2)
ISS stage, No. (%)			
I	23 (19.2)		29 (27.1)
II	53 (44.2)		43 (40.2)
III	38 (31.7)		34 (31.8)
Missing	6 (5.0)		1 (0.9)
R-ISS stage, No. (%)			
I	6 (5.0)		14 (13.1)
II	67 (55.8)		46 (43.0)
III	25 (20.8)		18 (16.8)
Missing	22 (18.3)		29 (27.1)
ECOG performance status, No. (%)			
0	47 (39.2)		51 (47.7)
1	46 (38.3)		42 (39.3)
2	17 (14.2)		10 (9.3)
3 or 4	5(4.2)		0 (0.0)
Missing	5 (4.2)		4 (3.7)
Double hit genetic,[a] No. (%)			
Double genetic hit	77 (64.2)	55 (56.1)	57 (53.3)
No double genetic hit	43 (35.8)	43 (43.9)	48 (44.9)
Missing	0 (0.0)	2 (1.9)	
SKY92 GEP,[a] No. (%)			
Present	72 (59.2)	72 (72.4)	82 (76.6)
Absent	27 (22.5)	27 (27.6)	24 (22.4)
Missing	22 (18.3)	1 (0.9)	
Double hit genetic AND SKY92 GEP,[b] No. (%)			
Double genetic hit + SKY92 GEP present		28 (28.6)	33 (30.8)
Double genetic hit only		27 (27.6)	24 (22.4)
SKY92 GEP present only		43 (43.9)	48 (44.9)
Missing		0	2 (1.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEP, gene expression profiling; ISS, International Staging System; R-ISS, revised ISS; UHiR, ultra-high-risk.

[a]All patients in MyeXI underwent cytogenetic screening (n = 590), and those with available RNA material also underwent combined GEP profiling (n = 302). To provide comparability of frequencies of molecular aberrations with OPTIMUM patients, an additional column has been added (right column for respective features double hit and SKY92 GEP) that refers to denominator of MyeXI UHiR patients who were identified by combined genetic and GEP profiling (n = 98 UHiR out of n = 302 screened).

[b]Frequencies for patients identified as UHiR by combined genetic and GEP profiling only (n = 98).

primary end point of the screening protocol. One hundred thirty-eight patients were meeting UHiR trial criteria, including nine (8%) with locally identified PCL (Fig 1).

All 138 patients were offered screening for OPTIMUM, with 107 patients providing informed consent and being eligible (Fig 1). Of the 107 patients, 57 (53%) had double hit genetics, 82 (77%) SKY92 GEP and 33 (31%) both double hit and SKY92 GEP (Table 1). All 107 OPTIMUM patients had at least one dose of trial treatment and are thus included in the analysis; 92 received an ASCT, 85 received consolidation 1 treatment after day 100-120 post-ASCT, and 80 received consolidation 2 analysis (Fig 1). Two interim analyses were conducted before completing recruitment, both surpassing the boundaries, therefore recruitment and follow-up continued as planned.

MyeXI Digital Comparator

In total, 590 MyeXI patients randomly assigned to CRD or KCRD had available stored material for risk profiling. Of those, 302, selected as a representative sample, were assessed for combined cytogenetic and SKY92 GEP risk profiling as per OPTIMUM. Additional 288 patients were assessed for cytogenetic information only, because of lack of stored RNA material for GEP profiling (Data Supplement [Supplementary Material]). In total, profiling

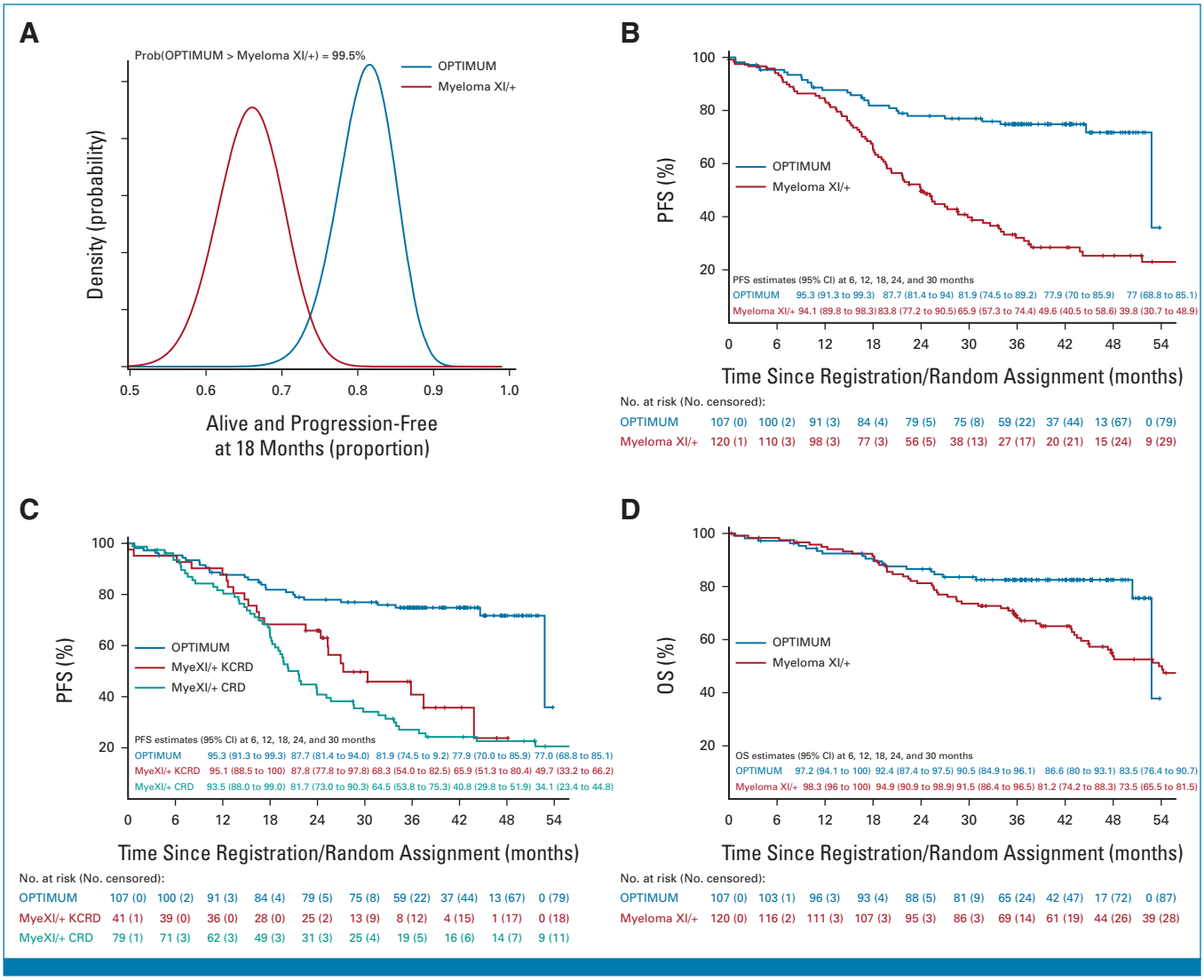

FIG 2. Primary end point analysis of PFS18m after registration for the OPTIMUM and MyeXI trials. (A) Probability density plots representing the certainty for PFS18m for MyeXI prior ($PFS18m_{MyeXI}$, solid red line) and OPTIMUM posterior ($PFS18m_{OPTIMUM}$, solid blue line); mode and 95% credible intervals from prespecified model; 0.66 (0.57-0.74) and 0.82 (0.74-0.88), respectively. There is a 99.5% probability of PFS18m being superior in OPTIMUM. (B) Kaplan-Meier curves for PFS for OPTIMUM and the MyeXI comparator data set with PFS estimates at 6, 12, 18, 24, and 30 months. (C) Kaplan-Meier curves for PFS for OPTIMUM and the MyeXI KCRd and CRd treatment arms shown separately with PFS estimate at 6, 12, 18, 24, and 30 months. (D) Kaplan-Meier curves for OS for OPTIMUM and the MyeXI comparator data set with OS estimates at 6, 12, 18, 24, and 30 months. KCRd, carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide; OS, overall survival; PFS, progression free-survival; PFS18m, progression free-survival at 18 months.

identified 120 patients with UHiR features and included in the MyeXI digital comparator. Baseline characteristics are summarized in Table 1. Three patients were excluded from PFS18m analysis because of unknown PFS.

Survival Analysis

One-hundred and three OPTIMUM patients had determinable PFS18m status; of these, 84 patients (81.7%) were alive and progression-free at 18 months after registration to OPTIMUM, compared with 77 of 117 evaluable patients (65.9%) in MyeXI. There was a 99.5% chance of PFS18m being superior for patients treated in OPTIMUM over those treated in MyeXI as per the Bayesian framework, surpassing the predefined 85% threshold for a meaningful improvement (Fig 2A). The results were consistent for a worst-case sensitivity analysis assuming the four OPTIMUM patients with missing PFS18m status had progressed. Further post hoc robustness analyses for specification of the digital comparator are presented in the Data Supplement (Supplementary Tables 2A, B, and 3A-C). The results were robust to the matching method with at least 74% probability for OPTIMUM results being superior to MyeXI in all scenarios (Data Supplement [Supplementary Table 3A]), although there was loss of precision as the effective sample size in MyeXI reduced to below 35.

Increasing separation of PFS curves in favor of OPTIMUM therapy was seen beyond 18 months. At 30 months, PFS estimate for OPTIMUM was 77.0% (95% CI, 68.8 to 85.1) versus 39.8% (95% CI, 30.7 to 48.9) for MyeXI (Fig 2B), with 49.7% (95% CI, 33.2 to 66.2) for KCRd and 34.1% for CRd (95% CI, 23.4 to 44.8) patients (Fig 2C). Estimates for OS at 30 months are 83.5% (95% CI, 76.4 to 90.7) and 73.5% (95% CI, 65.5 to 81.5) for OPTIMUM and MyeXI, respectively (Fig 2D).

At the time of analysis, 28 patients in OPTIMUM had a progression event (24 progressive disease and four deaths). Median PFS and OS are yet to be reached with a median follow-up of 41.2 months.

Response and Minimal Residual Disease

Maximum response at the end of induction and within 100 days post-ASCT is given in Table 2 and the Data Supplement (Supplementary Table 4). At the end of consolidation 1, 73 patients in the analysis achieved a complete response (CR; 68.2%), while 24 achieved a very good partial response (22.4%) and five achieved a PR (4.7%).

Forty-four of 107 patients (41.1%) achieved MRD negativity at the end of induction, increasing to 68 (63.6%) at 100-120 days post-ASCT (Table 2 and Data Supplement [Supplementary Table 5]). Reasons for nonevaluability are provided in the Data Supplement (Supplementary Material). Of the 68 patients with MRD-negative disease at day 100, 43 (63.2%) were also in CR at day 100, with 62 (91.2%) achieving a CR by the end of consolidation 1 (Table 2). Also, 84.0% of patients with MRD negativity 100-120 days post-ASCT were also MRD-negative at consolidation 2 (excluding 18/68 patients not evaluable at the end of consolidation 2).

TABLE 2. Patient Response as per IMWG Criteria and MRD Status at Key Treatment Time Points in the OPTIMUM Trial

Maximum Response	End of Induction, No. (%)	Day 100-120 Post-ASCT, No. (%)
CR	24 (22.4)	50 (46.7)
VGPR	63 (58.9)	43 (40.2)
PR	15 (14.0)	9 (8.4)
SD/NC	2 (1.9)	2 (1.9)
PD	1 (0.9)	1 (0.9)
Not evaluable	2 (1.9)	2 (1.9)

MRD	End of Induction, No. (%)	Day 100-120 Post-ASCT, No. (%)	End of Consolidation 2, No. (%)
MRD-	44 (41.1)	68 (63.6)	50 (46.7)
MRD+	43 (40.2)	15 (14.0)	4 (3.7)
Not evaluable	15 (14.0)	13 (12.1)	20 (18.7)
Time point not reached	5 (4.7)	11 (10.3)	33 (30.8)
Total	107 (100)	107 (100)	107 (100)

MRD at Day 100-120 Post-ASCT	Maximum Response, No. (%)	Day 100-120 Post-ASCT, No. (%)	End of Consolidation 1, No. (%)
MRD- (n = 68)	CR	43 (63.2)	62 (91.2)
	No CR	25 (36.8)	6 (8.8)
MRD+ (n = 15)	CR	4 (26.7)	9 (60.0)
	No CR	11 (73.3)	6 (40.0)

NOTE. Upper panel: maximum response as per IMWG criteria reached up to end of induction and day 100-120 post-ASCT. Middle panel: MRD status (cutoff for negativity 10^{-5}; Material and Methods), including nonevaluable patients, at the end of induction, day 100-120 post-ASCT, and end of consolidation 2. Lower panel: maximum response, binarized into CR or no CR, reached up to day 100-120 post-ASCT and end of consolidation 1, split up by MRD status at day100-120 post-ASCT, for those with a valid result.
Abbreviations: ASCT, autologous stem-cell transplantation; CR, complete response; MRD, minimal residual disease; PD, progressive disease; PR, partial response; SD/NC, stable disease/no change; VGPR, very good partial response.

Safety and Deliverability

AEs collected during intensified Dara-VRd consolidation 2 therapy are summarized in Table 3. Lead hematologic grade 3/4 AEs during intensified consolidation were thrombocytopenia (22.5%) and neutropenia (40.0%) and lead nonhematologic AE infection (12.5%), consistent with AEs observed during induction and consolidation without novel signals emerging (Table 3). AEs recorded throughout induction and consolidation 1 are summarized in the Data Supplement (Supplementary Tables 6 and 7, respectively).

TABLE 3. AEs Experienced During Consolidation 2 for the 80 Patients Who Completed at Least One Cycle of Consolidation 2 Treatment

	CTCAE Grade, No. (%)			
AE	1	2	3	4
Hematologic				
Anemia	44 (55.0)	14 (17.5)	3 (3.8)	0 (0.0)
Thrombocytopenia	31 (38.8)	16 (20.0)	18 (22.5)	4 (5.0)
Neutropenia	19 (23.8)	19 (23.8)	32 (40.0)	3 (3.8)
Infection				
Overall	5 (6.3)	23 (28.8)	10 (12.5)	2 (2.5)
Respiratory tract infection	4 (5.0)	21 (26.3)	8 (10.0)	2 (2.5)
Neurologic				
Peripheral neuropathy	50 (62.5)	9 (11.3)	2 (2.5)	0 (0.0)
GI				
Constipation	15 (18.8)	3 (3.8)	0 (0.0)	0 (0.0)
Diarrhea	26 (32.5)	8 (10.0)	1 (1.3)	0 (0.0)
Nausea	18 (22.5)	3 (3.8)	0 (0.0)	0 (0.0)
Vomiting	9 (11.3)	2 (2.5)	1 (1.3)	0 (0.0)
Other				
Fatigue	34 (42.5)	16 (20.0)	0 (0.0)	0 (0.0)
Pain—overall	31 (38.8)	13 (16.3)	2 (2.5)	0 (0.0)
Musculoskeletal pain	30 (37.5)	11 (13.8)	1 (1.3)	0 (0.0)
Cramp	15 (18.8)	4 (5.0)	0 (0.0)	0 (0.0)
Fever	16 (20.0)	1 (1.3)	0 (0.0)	0 (0.0)
Flu-like symptoms	11 (13.8)	7 (8.8)	0 (0.0)	0 (0.0)
Edema	16 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mood alterations	8 (10.0)	3 (3.8)	0 (0.0)	0 (0.0)
Rash	13 (16.3)	4 (5.0)	0 (0.0)	0 (0.0)
Hepatic	12 (14.1)	5 (5.9)	2 (2.4)	0 (0.0)
Renal	10 (12.5)	2 (2.5)	1 (1.3)	0 (0.0)

NOTE. AEs grade 1 or higher occurring in 10% or more patients and/or grade 3 higher occurring in 5% or more patients are listed. Infection and pain are recorded as maximum grade overall and further broken down occurring in three or more participants with subgroups not mutually exclusive.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Ninety-nine patients (92.5%) completed preplanned induction therapy, with five patients (4.7%) stopping treatment before completing one cycle. Of the 85 patients who started consolidation 1 treatment, 79 (92.9%) completed planned six cycles of therapy. Patients continued therapy throughout the first waves of the COVID-19 pandemic, at which time the majority were receiving consolidation 1 or 2 therapy. Information on dose reduction during consolidation 2 is presented in Table 4. Bortezomib was dose reduced in 31.0% and Len in 42.5% of patients before and/or during consolidation 2, whereas Dara was delivered at preplanned doses in nearly all (98.8%) of patients. Dose reductions during consolidation 1 are available in the Data Supplement (Supplementary Table 8).

TABLE 4. Dose Reductions During Consolidation 2 for the 80 Patients Who Completed at Least One Cycle of Consolidation 2 Treatment Including Dose Reductions Made Earlier in Therapy and Continued Throughout Consolidation 2

Modification of Therapy	Daratumumab, No. (%)	Bortezomib, No. (%)	Lenalidomide, No. (%)
No modification	79 (98.8)	48 (69.0)	46 (57.5)
Hematologic toxicity	0 (0)	11 (28.8)	17 (21.3)
Nonhematologic toxicity	0 (0)	26 (32.5)	20 (25.0)
Other	1 (1.3)	1 (1.3)	3 (3.8)

NOTE. The protocol encouraged early dose reductions in case of observed grade 1/2 adverse reactions throughout treatment, with the intention of reducing treatment interruption and discontinuation overall.

DISCUSSION

OPTIMUM demonstrates PFS of 77% for UHiR/PCL patients at 30 months, with median PFS not yet met after more than 3 years of follow-up, an outcome that is markedly superior by prespecified comparison with that of patients with molecularly mirrored UHiR MM from MyeXI, and further supported by an emerging positive OS signal for OPTIMUM. Intensified Dara-CVRd induction and ASCT resulted in a high rate of MRD negativity in UHiR/PCL post-ASCT, which was maintained in the majority of patients by Dara-VR(d) consolidation therapy. To our best knowledge, this is the first trial specific for UHiR NDMM and PCL showing a majority of sustained responses in this difficult-to-treat population with a follow-up beyond 3 years.

The SWOG1211 trial is, to our knowledge, currently the only contemporary comparative study for high-risk MM, randomly assigned patients on the basis of presence of single high-risk markers t(14;16), t(14;20), del(17p), amp(1q21), GEP high-risk signature, elevated serum lactate dehydrogenase or PCL and did not demonstrate an improvement in outcomes with addition of elotuzumab-VRD over VRD (median PFS 31.5 *v* 36.4 months, respectively).[41] An interim analysis of the first 50 patients of the single-arm, two-cohort (fit and unfit) phase II GMMG-CONCEPT trial for patients with del(17p), t(4;14), t(14;16), or amp(1q21) with International Staging System stage II or III disease showed an MRD-negativity rate of 62.5% after induction and a 12-month PFS rate of 79.6%, similar to OPTIMUM[42]; most patients were fit and received isatuximab-KRd, ASCT, and Isa-KR maintenance. Double hit/UHiR was reported in 26% of CONCEPT patients, compared with 53% in OPTIMUM. A recent sub-group analysis from the EMN02/HO95 trial, which was not published when OPTIMUM was designed, showed improved OS for tandem over single ASCT, in particular in patients with del(17p) tumors, with data from STAMINA being less conclusive for the high-risk subgroup.[43-45] The role of tandem ASCT in patients with

double hit or SKY92 high risk is currently unknown. The marked increase in MRD negativity after single ASCT in our trial suggests a benefit for high-dose alkylator therapy for some UHiR/PCL patients.

Incremental increase in PFS advantage for OPTIMUM over MyeXI, including over patients in receipt of KCRd, support the importance of intensified and prolonged consolidation for sustained disease control in UHiR MM.[46] Recently, the MASTER trial reported an elevated risk of early relapse for UHiR patients, even after sustained MRD negativity with Dara-KRd and subsequent protocol-defined treatment discontinuation, with a reported 2-year PFS of 58% for UHiR overall. Although the majority of OPTIMUM UHiR patients benefited from intensified Dara-CVRd induction, a small number of patients still relapsed early, in keeping with the findings from MASTER and CONCEPT, and highlighting the ongoing need for treatment innovation. Novel immune therapies such as T-cell engagers or chimeric antigen receptor–T cell therapies, which show unprecedented response rates, may provide such innovation, although more data on durability of responses in UHiR disease are required.[47-49]

Reassuringly, OPTIMUM results demonstrate manageable toxicities and high treatment deliverability for intensified post-ASCT Dara-VRd consolidation, even throughout pre-vaccine COVID-19 pandemic waves, which was facilitated by subcutaneous/oral formulations. Safety data overall are in keeping with other contemporary intensified quadruplet regimens, without new signals emerging in context of prolonged consolidation therapy.[4,50]

In addition, OPTIMUM results demonstrate the high success rate of combined diagnostic molecular genetics and GEP profiling in all-comers patients with suspected or confirmed MM from 39 NHS hospitals, highlighting the deliverability of molecularly stratified treatment for NDMM patients and supporting wider patient access to molecular diagnostics.

Our results also provide a framework for patient-centric digital comparator trials for well-defined, high-unmet-need subgroups of patients with cancer, whereby patient recruitment from the same NHS hospitals, and a mirrored molecular subgroup definition limited to NDMM for both trials contribute to control of bias and improvement of comparability.[27] The results are robust to model choices taken at the design stage for digital comparator data matching, confirmed by post hoc robustness analyses using well-recognized analytical matching approaches. Recruitment of OPTIMUM completed over 9 months ahead of projections, unusual for a fully academically sponsored and conducted trial, suggesting a high unmet need for risk-adapted therapy in NDMM. Although this is not a registration study, the high PFS and OS rates in OPTIMUM, which compare favorably with MyeXI, suggest Dara-CVRd induction and extended Dara-VR(d) post-ASCT consolidation is a novel effective treatment option for the clinical management of patients with UHiR MM and PCL, providing compelling evidence to support further evaluation of this treatment strategy.

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DISCLAIMER

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

EQUAL CONTRIBUTION

S.R.B. and M.W.J. contributed equally as last authors.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Any requests for individual participant data will be reviewed by the trial management group in the first instance and considered after completion of all primary and secondary end point analyses of the trial. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, and Dexamethasone as Induction and Extended Consolidation Improves Outcome in Ultra-High-Risk Multiple Myeloma

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