Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma

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ABSTRACT

PURPOSE The GMMG-CONCEPT trial investigated isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in transplant-eligible (TE) and transplant-noneligible (TNE) patients with newly diagnosed multiple myeloma (NDMM) with exclusively high-risk disease for whom prospective trials are limited, aiming to induce minimal residual disease (MRD) negativity.

METHODS This academic, investigator-initiated, multicenter, phase II trial enrolled patients with high-risk NDMM (HRNDMM) defined by mandatory International Staging System stage II/III combined with del17p, t(4;14), t(14;16), or more than three 1q21 copies as high-risk cytogenetic aberrations (HRCAs). Patients received Isa-KRd induction/consolidation and Isa-KR maintenance. TE patients received high-dose melphalan. TNE patients received two additional Isa-KRd cycles postinduction. This prespecified interim analysis (IA) reports the primary end point, MRD negativity ($<10^{-5}$, next-generation flow), at the end of consolidation. The secondary end point was progression-free survival (PFS).

RESULTS Among 125 patients with HRNDMM (TE—intention-to-treat [ITT]-IA, 99; TNE-ITT, 26) of the IA population for the primary end point, the median age was 58 (TE-ITT-IA) and 74 (TNE-ITT) years. Del17p was the most common HRCA (TE, 44.4%; TNE, 42.3%); about one third of evaluable TE/TNE patients presented two or more HRCAs, respectively. The trial met its primary end point with MRD negativity rates after consolidation of 67.7% (TE) and 54.2% (TNE) of patients. Eighty-one of 99 TE-ITT-IA patients reached MRD negativity at any time point (81.8%). MRD negativity was sustained for ≥1 year in 62.6% of patients. With a median follow-up of 44 (TE) and 33 (TNE) months, median PFS was not reached in either arm.

CONCLUSION Isa-KRd effectively induces high rates of sustainable MRD negativity in the difficult-to-treat HRNDMM population, regardless of transplant status, translating into a median PFS that was not yet reached after 44/33 months.

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INTRODUCTION

Clinical outcomes in multiple myeloma (MM) have markedly improved over the past decade with the implementation of novel agents and continuous treatment approaches.[1-6] Adding anti-CD38 monoclonal antibodies to backbone regimens has led to unprecedented outcomes for transplant-eligible (TE) and transplant-noneligible (TNE) patients.[2-4,7] However, outcomes remain dismal for patients with MM with high-risk disease. As was recently reported, patients with higher Second Revision of the International Staging System (R2-ISS) stages III and IV show a median progression-free survival (PFS) of only 30 and 20 months, respectively.[8]

Achievement of minimal residual disease (MRD) negativity is currently the strongest outcome predictor[9-12]; therefore, inducing and maintaining MRD-negative responses is of particular importance in HRMM. Nonetheless, patients with HR disease have been underrepresented in clinical trials.

CONTEXT

Key Objective

What is the impact of using extended quadruplet treatment with isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) on achieving minimal residual disease (MRD) negativity in patients with difficult-to-treat high-risk newly diagnosed (ND) multiple myeloma, regardless of age and transplant eligibility, and how does this translate into progression-free survival (PFS)?

Knowledge Generated

MRD negativity rates after consolidation were 67.7% for transplant-eligible (TE) and 54.2% for transplant-noneligible (TNE) patients, and sustained MRD negativity for ≥1 year was observed in 62.6% and 46.2% (TE and TNE, respectively). Median PFS was not reached in either arm after a median follow-up of 44 (TE) and 33 (TNE) months.

Relevance *(S. Lentzsch)*

Isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRD) is a well-tolerated and very effective induction treatment for newly diagnosed high-risk multiple myeloma, resulting in deep remissions. Future prospective studies need to determine how daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (D-CVRD) tested in the OPTIMUM trial or daratumumab, carfilzomib, lenalidomide, dexamethasone (Dara-KRD) tested in the IFM 2018-04 trial compared to the here reported Isa-KRD data in the population of patients with high-risk multiple myeloma.*

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

Most data on HRMM come from subgroup analyses of clinical studies or retrospective/observational studies, with few prospective trials studying only patients with HRMM, which are needed to help determine the optimal treatment strategy for this population.

The phase II GMMG-CONCEPT trial (ClinicalTrials.gov identifier: NCT03104842) was designed to study patients with newly diagnosed (ND) HRMM (TE and TNE) treated with the quadruplet combination of isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in induction/consolidation, followed by triplet maintenance (Isa-KR). The primary objective was to evaluate MRD negativity ($<10^{-5}$, next-generation flow [NGF]) after consolidation. The secondary objective was to assess PFS.

METHODS

Patients

Adult patients with HR NDMM were eligible, with HR defined by ISS stage II or III combined with ≥1 of the following: del17p (in >10% of purified cells), t(4;14), t(14;16), or more than three 1q21 copies (amplification 1q21 [amp1q21]) as high-risk cytogenetic aberrations (HRCAs); primary plasma cell leukemia was eligible. An Eastern Cooperative Oncology Group performance status of 0-3 and adequate organ function (eg, creatinine clearance ≥30 mL/min) at the time of inclusion were required. To include NDMM with aggressive disease and immediate need for treatment, one prior cycle of any anti-MM therapy was allowed; HRNDMM patients with oligosecretory or nonsecretory disease but measurable bone lesions or extramedullary manifestations were also eligible. All patients provided written informed consent. Detailed inclusion/exclusion criteria are shown in Appendix Table A1 (online only).

Trial Design and Treatment

GMMG-CONCEPT is an academic, investigator-initiated, nonrandomized, multicenter, phase II clinical trial conducted in 17 German sites with two treatment arms according to eligibility for high-dose therapy (HDT). In arm A, TE patients received six cycles of Isa-KRd induction (with stem-cell collection after cycle 3), followed by HDT and autologous stem-cell transplantation (ASCT). Consolidation consisted of four cycles of Isa-KRd, and maintenance was 26 cycles of Isa-KR. Patients noneligible for HDT or age older than 70 years entered arm B with identical induction, consolidation, and maintenance and two additional cycles of Isa-KRd instead of HDT-ASCT.

Induction and consolidation cycles lasted 28 days, with isatuximab 10 mg/kg given intravenously (IV) once daily on days 1 and 15; carfilzomib 36 mg/m^2 (IV) once daily on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg orally once daily on days 1-21; and weekly dexamethasone 40 mg (orally/IV once daily; 20 mg if older than 75 years). Further specifications and maintenance treatment doses are listed in Appendix 1.

Patients in the first cohort were enrolled from August 2017 to April 2020. The trial was amended in 2021 to recruit a second cohort of TE patients (Appendix 1).

End Points and Assessments

The primary end point is the proportion of patients reaching MRD negativity ($<10^{-5}$, NGF) at the end of consolidation. Secondary end point is PFS, defined as the time from enrollment to progression or death, whichever occurs first. Tertiary end points include overall response rate (ORR), defined as the proportion of patients with partial responses (PRs) or better; complete response (CR) or better; and overall survival (OS), defined as the time from enrollment to death from any cause.

MRD assessment was mandatory at the end of consolidation and every 6 months thereafter. Before the end of consolidation, MRD assessment was recommended in case of very good PR (VGPR) or better.

MRD assessments from the first pull of bone marrow aspirate were measured in a central laboratory using a standardized and validated eight-color flow panel. MRD results and traditional response assessments are reported according to International Myeloma Working Group (IMWG) consensus criteria.[13]

Duration of sustained MRD negativity is defined as the time from first MRD-negative until the last MRD-negative or first MRD-positive assessment, depending on what ends the sequence of MRD-negative assessments with no positive in between.

Trial Oversight

The trial was approved by competent authorities and ethics committees and was conducted according to the Good Clinical Practice Guidelines of the International Conference on Harmonisation and the ethical principles described in the 2013 Declaration of Helsinki. The study is registered at ClinicalTrials.gov (identifier: NCT03104842).

University Medical Center Hamburg-Eppendorf is the academic sponsor of this trial and is solely responsible for study design, conduct, data collection, and analysis. A Data Safety Monitoring Board provided external independent oversight of the trial.

Statistical Analysis

Sample size was calculated for primary and secondary end points in arm A and for primary end point in arm B; the details are provided in Appendix 1.

The primary end point (MRD negativity rate at the end of consolidation) was tested on the MRD analysis population, defined by all intention-to-treat (ITT) patients, except those with technical evaluation failures. For arm A, a group sequential design was applied with a single-efficacy interim analysis (IA) on the basis of the first 93 patients of the MRD analysis population (according to trial allocation; Appendix Fig A1) on $\alpha = 3.05\%$ and a final analysis on $\alpha = 3.0\%$ (Pocock α-spending for cumulative one-sided significance level of 5%), if the test result was not significant at the time of IA. An exact one-sided binomial test was applied to test the null hypothesis (MRD negativity rate ≤50% [arm A] and ≤30% [arm B]).

The secondary end point (PFS) was tested on the ITT-IA population (first 99 ITT patients [Appendix Fig A1]) at the time of IA of the primary end point on a one-sided $\alpha = .0001$ and the final analysis on $\alpha = .0499$. The null hypothesis, median PFS ≤25 months, was tested by a one-sample one-sided log-rank test (OSLRT).[14] A fixed-sequence testing procedure was used for the primary and secondary end point analyses. For arm B, the null hypothesis (median PFS ≤25 months) was tested by an OSLRT on one-sided $\alpha = 5\%$.

The 95% CI boundaries on the basis of the Wilson method[15] are presented for the MRD negativity rates. Kaplan-Meier (KM) estimates and corresponding 95% CIs for survival and IMWG responses were computed for each study arm. Because MRD status changes over time,[16] we performed a time-varying Cox regression analysis[17] to investigate the prognostic impact of the first achievement of MRD negativity (any time on study) on PFS: Hazard ratios (HRs) and 95% CIs provide an estimate of the risk for PFS from MRD negativity compared with the state of non-negative MRD (MRD-positive, not assessable, or without assessment). The *P* value was derived by the Wald test. Illustration of survival with respect to MRD status is done using Bernasconi-Simon-Makuch plots.[18]

As sustained MRD negativity for ≥6 or ≥12 months cannot be achieved during the first 6 or 12 months on study, a landmark analysis providing KM estimates for survival was performed evaluating the difference in PFS from maintenance start comparing patients with sustained MRD negativity with those without until consolidation end. Analogously, we investigated PFS with respect to MRD negativity at the end of consolidation (primary end point) to adjust for potential bias in survival estimates because of nonmandatory MRD assessment before consolidation end.

Safety End Points

Safety analyses were conducted for all ITT patients receiving ≥1 trial medication dose. Medical Dictionary for Regulatory Activities coding version 26.0 was used; in case of multiple occurrences of the same adverse event (AE) term, the maximum grade was reported. Definitions of specific preferred terms are provided in the Appendix (Table A3). The data cutoff was December 1, 2022.

RESULTS

Patients

Of 153 patients with HRNDMM enrolled in the first cohort, 127 TE patients entered arm A and 26 TNE patients arm B.

According to the trial design, the ITT population for planned IA included 99 TE and all 26 TNE patients (Appendix Fig A1). The median age of TE and TNE patients was 58 (range, 35-73) and 74 (range, 64-87) years, respectively. Fifty-eight patients (46.4%) had ISS stage III; 66 (52.8%) patients were R2-ISS stages III/IV; patient characteristics are depicted in Table 1 (and in Appendix Table A2 for non-ITT-IA patients).

Del(17p) was the most common HRCA, followed by t(4;14) and amp1q21. About one third of evaluable patients had ≥2 HRCAs; in eight TE and two TNE patients, ≥1 HRCA was not tested for; therefore, patients could not be uniquely categorized.

Seventy-three of 99 TE and 16 of 26 TNE patients completed consolidation and started maintenance. Patient disposition is shown in Figure 1. The most common reasons for treatment discontinuation through consolidation were disease progression (n = 12) and death (n = 7).

IMWG Response and MRD Negativity

Of 99 TE patients, 72.8% (n = 72) achieved CR/stringent CR (sCR) until the end of consolidation, and 18.2% (n = 18) achieved VGPR, with an ORR of 94.9%. In TNE patients, CR/sCR, VGPR, and ORR rates were 57.7%, 30.8%, and 88.5%, respectively. Responses deepened over time (Figs 2A and 2B).

Analysis of the primary end point included 93 TE patients of the IA population and 24 available TNE patients (MRD analysis population; Appendix Fig A1). At consolidation end, 63 (67.7%) TE patients were MRD-negative and three (3.2%) were MRD-positive. Twenty-three (24.7%) patients did not reach consolidation end; four (4.3%) had missing samples. Fifty-three MRD-negative patients were in CR/sCR and 10 in VGPR; MRD-positive patients had VGPR, CR, and sCR (one each).

For TNE patients, 13 (54.2%) were MRD-negative (CR/sCR, 11; VGPR, 2), and 11 (45.8%) did not reach consolidation end. The primary end point of the study was met in both arms (TE, $P = .004$; TNE, $P = .012$; Fig 2C); the trial is ongoing per DSMB recommendation.

Of the 99 ITT-IA-TE patients, 81 reached MRD negativity at any time point (81.8%). MRD-negative status was sustained for ≥6 and ≥12 months in 72 and 62 patients, respectively, resulting in sustained MRD negativity rates of 72.7% and 62.6% (Figs 2D and 2F).

The results in TNE patients were slightly lower; 18 (69.2%) patients reached MRD negativity at any time point, with 14 (53.8%) and 12 (46.2%) sustained MRD-negative responses for ≥6 and ≥12 months, respectively (Figs 2E and 2F).

PFS and OS

With a median follow-up of 44 (TE) and 33 (TNE) months, median PFS was not reached in either arm (Figs 3A and 3B). The study met its secondary end point of PFS (TE, $Z_{OSLR} = 5.75$, $P < .0001$; TNE, $Z_{OSLR} = 1.95$, $P = .0259$).

Respective PFS rates after 1, 2, and 3 years were 86.4% (95% CI, 80.5 to 92.6), 78.3% (95% CI, 71.4 to 85.9), and 68.9% (95% CI, 61.2 to 77.7) for TE patients (Fig 3A) and 75.1% (95% CI, 59.7 to 94.5), 62.6% (95% CI, 46.0 to 85.3), and 58.4% (95% CI, 41.7 to 81.9) for TNE patients (Fig 3B).

Similar to PFS, median (m)OS was not reached in either study arm after 44 (TE) and 35 (TNE) months of follow-up. Respective 1-year and 2-year OS rates of 92% (95% CI, 87.3 to 96.9) and 83.9% (95% CI, 77.7 to 90.6) were observed in TE patients (Fig 3C), and 83.5% (95% CI, 69.6 to 99.7) and 71.0% (95% CI, 55.0 to 91.6) in TNE patients (Fig 3D).

Influence of Different HR Parameters on MRD Status and PFS

Subgroup analyses regarding various HR features were performed for TE patients for the primary end point in an ITT approach. Subgroups with the lowest MRD negativity rates were patients with an elevated baseline lactate dehydrogenase (LDH; MRD negativity: 45.5% [95% CI, 26.9 to 65.3]), with t(14;16) (56.2% [95% CI, 33.2 to 76.9]), harboring ≥2 HRCAs (57.1% [95% CI, 39.1 to 73.5]) or amp1q21 (58.6% [95% CI, 40.7 to 74.5]). However, MRD negativity was still achieved in approximately half or more of these patients (Appendix Fig A2).

Regarding the impact of these features on survival, univariate Cox regression showed impaired PFS for patients with elevated LDH (HR, 3.18 [95% CI, 1.63 to 6.19]), ≥2 HRCAs (HR, 2.10 [95% CI, 1.09 to 4.04]), del17p (HR, 1.34 [95% CI, 0.71 to 2.54]), or R2-ISS stages III/IV (HR, 2.11 [95% CI, 1.09 to 4.08]; KM estimates Figs 4A-4C, respectively), whereas no major differences were seen for other HRCAs (Appendix Fig A3).

Prognostic Impact of MRD Status on PFS

To investigate the prognostic impact of MRD negativity compared with non-negative MRD state on PFS in TE patients, we performed a time-varying Cox regression analysis, as MRD negativity (might) occur along treatment and compete with progression/death events. Univariate time-varying Cox regression showed a prognostic PFS benefit (HR, 0.118 [95% CI, 0.049 to 0.289]; $P = .0027$), estimating the risk for PFS events under MRD negativity versus non-MRD negativity (Fig 4D). Multivariable time-varying Cox regression analysis was performed to adjust for the influence of R2-ISS components (Appendix Table A4). To address potential bias in the outcome of MRD assessments before the end of consolidation, a landmark analysis investigating the differences between MRD-negative and MRD–non-negative patients at consolidation end with respect to PFS was performed (HR, 0.44 [95% CI, 0.14 to 1.38]; $P = .160$; Fig 4E). A landmark analysis from

TABLE 1. Baseline Characteristics Are Shown for ITT Patients Separately for Arms A (TE patients) and B (TNE patients)

Characteristic	TE Patients (n = 99)	TNE Patients (n = 26)	Total (N = 125)
Age, years, median (range)	58 (35-73)	74 (64-87)	62 (35-87)
Sex, No. (%)			
Female	52 (52.5)	14 (53.8)	66 (52.8)
Male	47 (47.5)	12 (46.2)	59 (47.2)
ECOG, No. (%)			
0-1	85 (85.9)	18 (69.2)	103 (82.4)
2-3	14 (14.1)	7 (26.9)	21 (16.8)
Missing	—	1 (3.8)	1 (0.8)
Disease isotype, No. (%)			
IgG	43 (43.4)	10 (38.5)	53 (42.4)
IgA	38 (38.4)	12 (46.2)	50 (40.0)
IgM	0 (0)	1 (3.8)	1 (0.8)
Light chain	18 (18.2)	3 (11.5)	21 (16.8)
Light chain, No. (%)			
Kappa	65 (65.7)	15 (57.7)	80 (64.0)
Lambda	34 (34.3)	11 (42.3)	45 (36.0)
Oligosecretory or nonsecretory disease, No. (%)	8 (8.1)	2 (7.7)	10 (8.0)
ISS stage, No. (%)			
II	53 (53.5)	13 (50.0)	66 (52.8)
III	45 (45.5)	13 (50.0)	58 (46.4)
R2-ISS, No. (%)			
I	8 (8.1)	0 (0)	8 (6.4)
II	32 (32.3)	10 (38.5)	42 (33.6)
III	26 (26.3)	9 (34.6)	35 (28.0)
IV	22 (22.2)	5 (19.2)	27 (21.6)
Not classifiable	11 (11.1)	2 (7.7)	13 (10.4)
R2-ISS dichotomized, No. (%)			
I + II	48 (48.5)	10 (38.5)	58 (46.4)
III + IV	51 (51.5)	15 (57.7)	66 (52.8)
Not classifiable	0 (0)	1 (3.8)	1 (0.8)
Cytogenetic aberration, No. (%)			
del(17p)	44 (44.4)	11 (42.3)	55 (44.0)
t(4;14)	42 (42.4)	6 (23.1)	48 (38.4)
t(14;16)	17 (17.2)	2 (7.7)	19 (15.2)
amp1q21	31 (31.3)	14 (53.8)	45 (36.0)
HRCAs, No. (%)			
1 HRCA	60 (60.6)	17 (65.4)	77 (61.6)
≥2 HRCAs	31 (31.3)	7 (26.9)	38 (30.4)
Not classifiable[a]	8 (8.1)	2 (7.7)	10 (8.0)
MM lytic bone lesions, No. (%)			
0	15 (15.2)	4 (15.4)	19 (15.2)
1-2	10 (10.1)	1 (3.8)	11 (8.8)
≥3	71 (71.7)	20 (76.9)	91 (72.8)
Extramedullary manifestation, No. (%)			
Bone related	12 (12.1)	5 (19.2)	17 (13.6)
Soft tissue	9 (9.1)	1 (3.8)	10 (8.0)
Elevated LDH (>ULN), No. (%)	24 (24.2)	8 (30.8)	32 (25.6)
Therapy before enrollment, No. (%)	31 (31.3)	11 (42.3)	41 (33.6)
Plasma cell infiltration, % median (range)	60 (0-100)	50 (5.5-100)	60 (1-100)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HRCA, high-risk cytogenetic aberration; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; ISS, International Staging System; ITT, intention-to-treat; LDH, lactate dehydrogenase; MM, multiple myeloma; R2-ISS, Second Revision of the International Staging System; TE, transplant-eligible; TNE, transplant-noneligible; ULN, upper limit of normal.
[a]In eight TE and two TNE patients, at least one HRCA was not tested for; therefore, patients could not be uniquely categorized as having 1 or ≥2 HRCA.

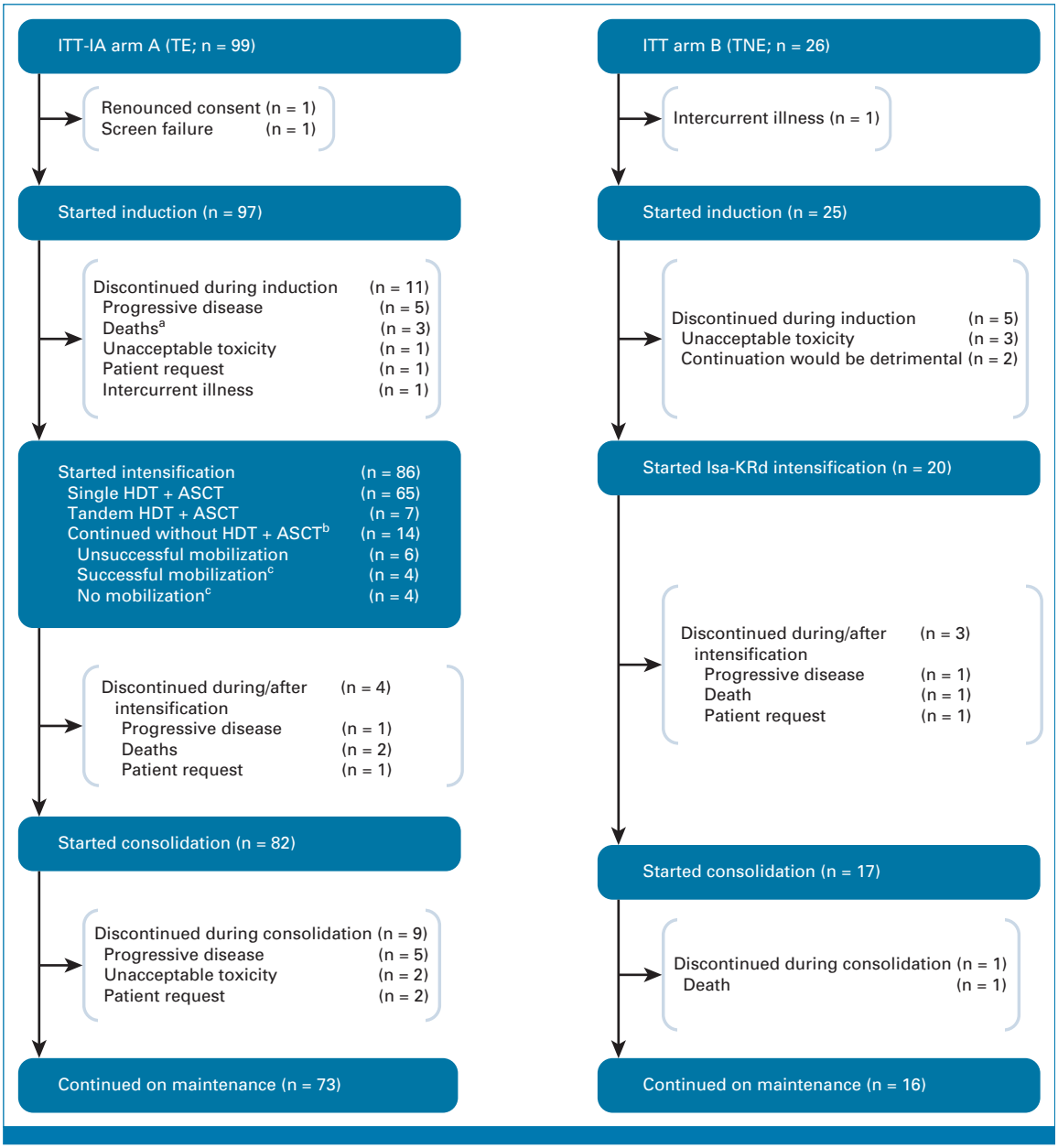
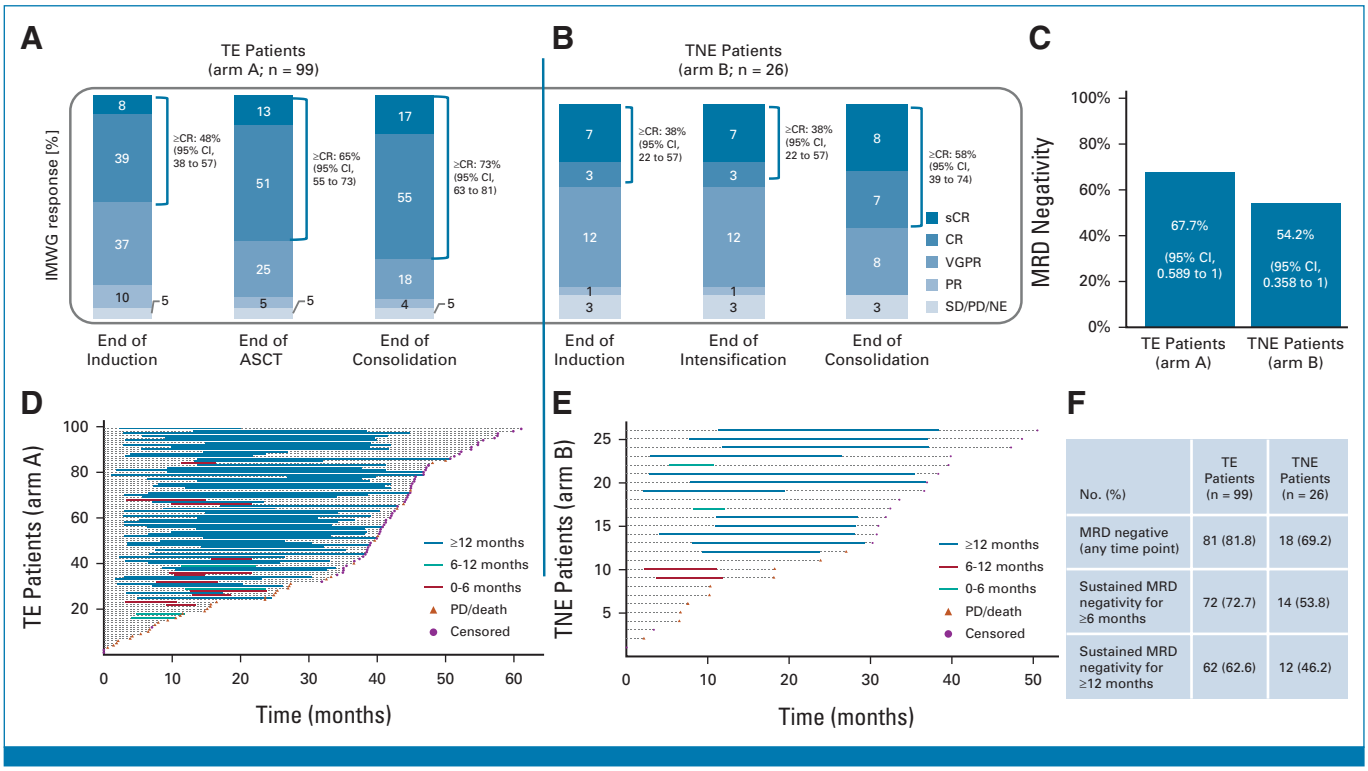


FIG 1. Patient disposition until the end of consolidation. [a]One of the three deaths occurred during mobilization. [b]All patients not undergoing HDT + ASCT received two additional cycles of Isa-KRd (analogous to arm B). [c]No HDT-ASCT because of investigator decision or patient wish. ASCT, autologous stem-cell transplantation; HDT, high-dose therapy; IA, interim analysis; Isa-KRd, isatuximab, carfilzomib, lenalidomide, and dexamethasone; ITT, intention-to-treat; TE, transplant-eligible; TNE, transplant-noneligible.

maintenance start was performed to investigate the prognostic impact of sustained MRD negativity ≥6 months on PFS and showed a HR of 0.85 (95% CI, 0.33 to 2.20; $P = .738$; Fig 4F).

Safety

Isa-KRd treatment was tolerable, and side effects were manageable, with a toxicity profile similar to previous reports. Overall, 92.6% of patients experienced at least one AE. AEs of higher Common Terminology Criteria for Adverse Events grades (≥3) were mainly hematologic (neutropenia, 36.9%; thrombocytopenia, 24.6%; leukopenia, 20.5%); infections (mainly respiratory) were the most common higher-grade nonhematologic AEs (27.9%; Table 2; Appendix Tables A5 and A6). Toxicity profiles were comparable between TE and TNE patients, with the exception of more frequent higher-grade cardiac events in TNE patients (TE, n = 2 [1.6%]; TNE, n = 5 [20%]). Six patients (TE, n = 3; TNE, n = 3) discontinued because of treatment-related AEs.



No. (%)	TE Patients (n = 99)	TNE Patients (n = 26)
MRD negative (any time point)	81 (81.8)	18 (69.2)
Sustained MRD negativity for ≥6 months	72 (72.7)	14 (53.8)
Sustained MRD negativity for ≥12 months	62 (62.6)	12 (46.2)

FIG 2. Best response according to the IMWG (A and B) according to treatment phase in (A) TE and (B) TNE patients, rates of greater than or equal to CR and 95% CIs are added. (C) MRD negativity status at the end of consolidation (primary end point). 95% CIs refer to the one-sided binomial test result of the primary end point, testing the observed MRD negativity rate against 50% and 30%, respectively. (D and E) Swimmer plots showing achievement and sustainment of MRD negativity (next-generation flow; MRD $<10^{-5}$) for (D) TE and (E) TNE patients. (F) Sustained MRD negativity for ≥6 months or ≥12 months in both study arms. ASCT, autologous stem-cell transplantation; CR, complete response; IMWG, International Myeloma Working Group; MRD, minimum residual disease; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; TE, transplant-eligible; TNE, transplant-noneligible; VGPR, very good partial response.

DISCUSSION

Treatment with Isa-KRd in the GMMG-CONCEPT trial led to high MRD negativity rates at any time point of 81.8% and 69.2% in solely HRNDMM TE and TNE patients, respectively. MRD negativity was sustained for ≥1 year in 62.6% (TE) and 46.2% (TNE) of patients and translated into a median PFS that was not reached after 44 (TE) and 33 (TNE) months of follow-up, respectively. To our knowledge, this study was among the first to include only patients with HRMM, without limiting on the basis of age or transplant eligibility, and is also the first to report the use of the quadruplet Isa-KRd in extended induction, consolidation, and Isa-KR maintenance resulting in deep and durable responses in this difficult-to-treat population.

Isa-KRd was tolerable and feasible with a safety profile consistent with similar regimens. In this single-arm trial, there was no evidence that adding isatuximab to the KRd backbone led to increased higher-grade toxicities.

Although HR definitions vary among clinical trials,[6,19–21] it was recently shown in the R2-ISS that ISS stages II and III confer the highest risk, along with del(17p) and elevated LDH,[8] which is consistent with our findings. R2-ISS stage III patients have an mPFS of 30/19 months (training/validation set), whereas R2-ISS stage IV patients have an mPFS of 20/15 months.[8] In our study, over half of patients were R2-ISS stage III/IV, yet mPFS and mOS were not reached after >3 years. Similar promising outcomes for PFS and MRD negativity were recently reported from OPTIMUM/MUKnine (ClinicalTrials.gov identifier: NCT03188172) with daratumumab, cyclophosphamide, bortezomib, lenalidomide, and dexamethasone quintuplet induction in patients with HRNDMM, showing MRD negativity rates of 63.6% after ASCT and a 30-month PFS rate of 77%.[21] In OPTIMUM, 27.1% of patients had ISS stage I and 53% harbored ≥2 HRCAs defined as t(4;14)/t(14;16)/t(14;20), del(1p), gain(1q), and del(17p).[21] In our trial, no ISS stage I patients were included, and 30.4% had ≥2 HRCAs of t(4;14)/t(14;16), amp(1q), and del(17p). Both OPTIMUM and CONCEPT showed the potency and feasibility of up-front, intensive, multidrug regimens incorporating anti-CD38 antibodies for inducing MRD-negative remission in HR patients.

High MRD negativity rates have been reported by recent NDMM trials incorporating anti-CD38 antibodies in all-comer populations. In the phase II GRIFFIN trial

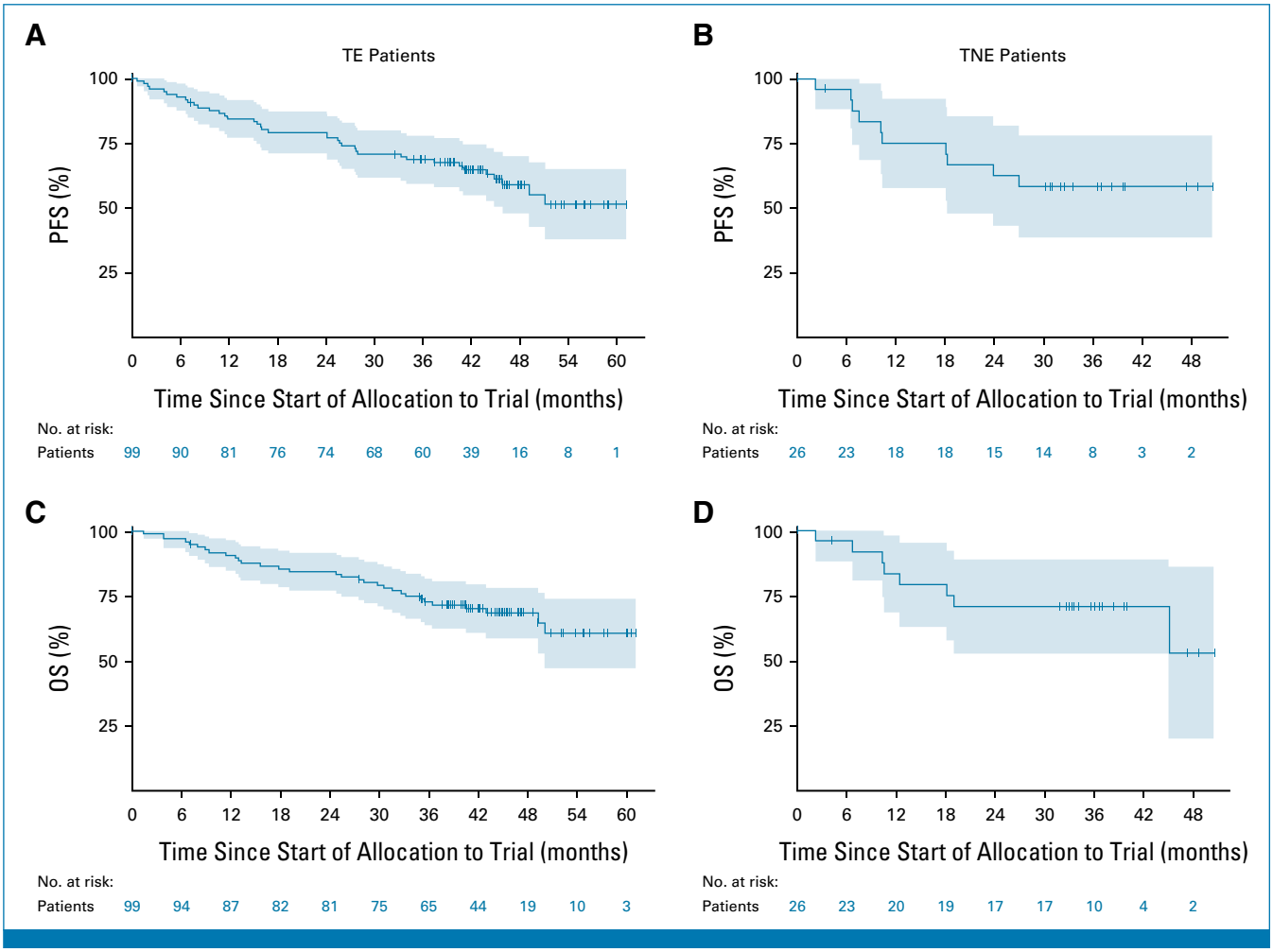


FIG 3. Kaplan-Meier plots for PFS in (A) TE and (B) TNE patients. OS in (C) TE and (D) TNE patients. OS, overall survival; PFS, progression-free survival; TE, transplant-eligible; TNE, transplant-noneligible.

(ClinicalTrials.gov identifier: NCT02874742), 51.0% treated with quadruplet daratumumab, lenalidomide, bortezomib, and dexamethasone (D-RVd) achieved MRD negativity at any point during the study, whereas a 50.0% rate was observed after induction in the phase III GMMG-HD7 trial (ClinicalTrials.gov identifier: NCT03617731) using isatuximab-RVd.[7,22]

Daratumumab-KRd (D-KRd) was evaluated in the MANHATTAN trial (ClinicalTrials.gov identifier: NCT03290950), resulting in an MRD negativity rate of 71% after eight cycles (thereafter, patients could undergo HDT-ASCT or continue with maintenance),[23] leading to National Comprehensive Cancer Network's recommendation of the regimen for TE NDMM.[24] Using D-KRd up to 12 cycles but including HDT-ASCT, an 80% MRD negativity rate was described in the MASTER trial (ClinicalTrials.gov identifier: NCT03224507) in a population with 39% ISS stage I and 43% not harboring HRCAs[19] versus 81.8% of exclusively HR TE patients in the CONCEPT trial achieving MRD negativity. MASTER also showed that early achievement of MRD negativity was beneficial versus later achievement with regard to MRD resurgence, underlining the importance of effective up-front induction.[19]

Albeit from a small cohort of TNE patients, the 69.2% MRD negativity rate and mPFS that was not reached after 33 months in CONCEPT compare favorably with the KRd-only arm in the FORTE trial, reporting a 29-month mPFS,[20] despite the older age and reduced fitness in CONCEPT. The same holds true for MAIA (ClinicalTrials.gov identifier: NCT02252172) and ALCYONE (ClinicalTrials.gov identifier: NCT02195479) subgroup analyses, with a 41.3% 3-year PFS rate for HRNDMM TNE patients with daratumumab-based regimens (daratumumab-lenalidomide-dexamethasone or daratumumab-bortezomib-melphalan-prednisone)[25] compared with a 58.4% 3-year PFS rate in CONCEPT.

Ongoing/upcoming trials focusing on MRD-driven approaches, such as MIDAS (ClinicalTrials.gov identifier: NCT04934475), PERSEUS (ClinicalTrials.gov identifier: NCT03710603), RADAR (ISCRTN46841867), and ADVANCE (ClinicalTrials.gov identifier: NCT04268498), will further elucidate the role of MRD dynamics and possibly tailor treatment, at least for the non-HR patient population.[26-29]

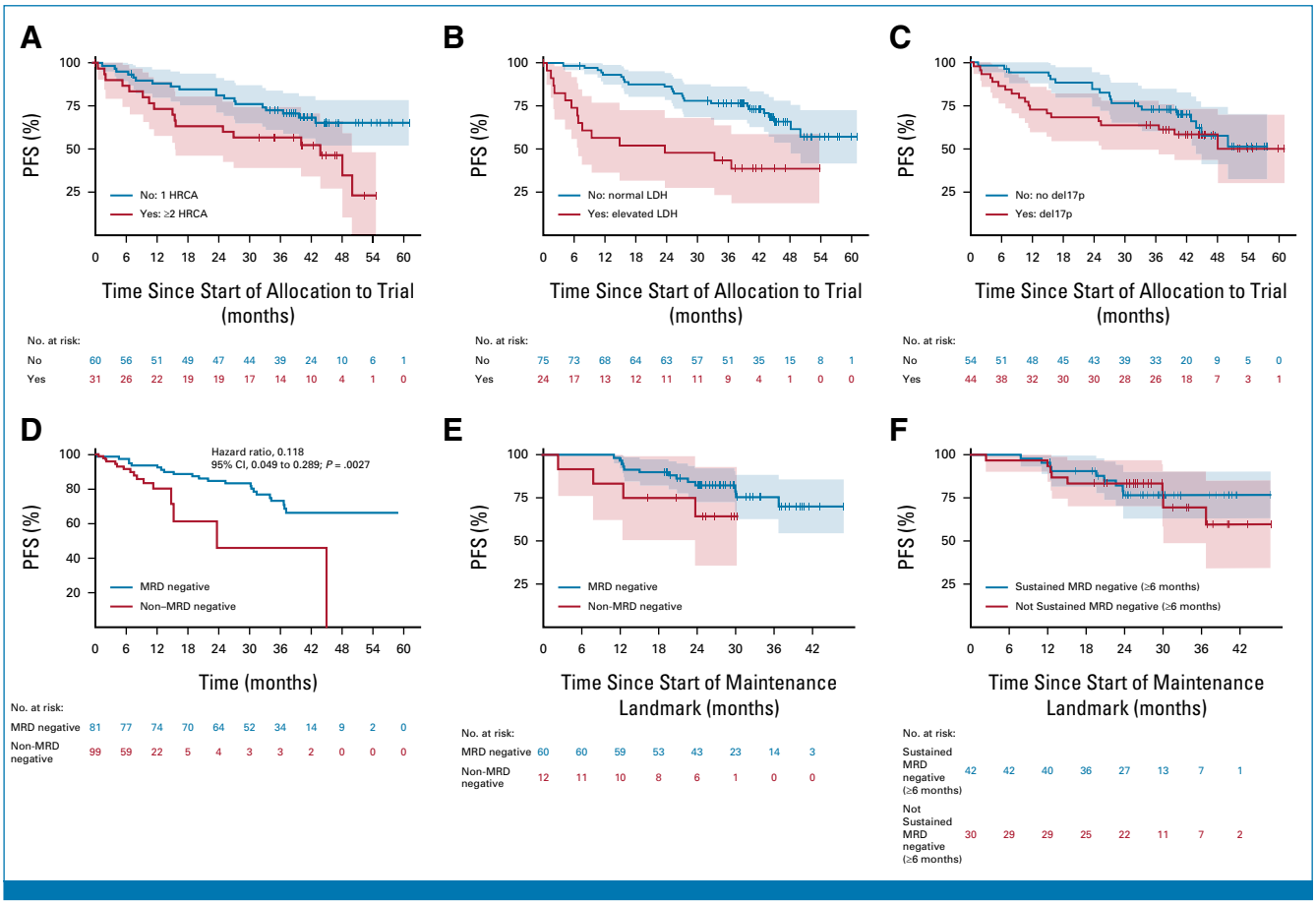


FIG 4. KM plots for PFS in TE patients according to the presence (red) or absence (blue) of (A) two or more HRCAs, (B) elevated LDH, or (C) del17p. (D) Adjusted Simon-Makuch (Bernasconi-SM) plot for TE patients: estimation of expected PFS under the state of first achievement of MRD negativity on study (blue) compared with the state waiting for MRD negativity (red). Blue curve can be interpreted as the expected PFS of a patient to be known achieving MRD negativity on study (alternatively to be interpreted as the hazard of PD/death under the state of MRD negativity). Red curve can be interpreted as the expected PFS of a patient who is assumed to fail achievement of MRD negativity (alternatively to be interpreted as the hazard of PD/death while waiting for MRD negativity). (E and F) KM plots for PFS from the landmark start of maintenance therapy according to (E) MRD outcome assessed at the end of the consolidation or (F) the achievement of sustained MRD negativity for ≥6 months until the end of consolidation. HRCAs, high-risk cytogenic aberrations; KM, Kaplan-Meier; LDH, lactate dehydrogenase; MRD, minimum residual disease; PD, progressive disease; PFS, progression-free survival; TE, transplant-eligible.

Although the role of high-dose melphalan in the frontline setting has been questioned, it is still standard for HR patients because of better survival outcomes.[6,30,31] In DETERMINATION (ClinicalTrials.gov identifier: NCT01208662), HR patients undergoing HDT-ASCT had an mPFS of 55 months versus 17.1 months for those without[6]; a subgroup analysis from FORTE confirmed the beneficial PFS effect of KRd + ASCT versus KRd in HR patients.[30] As we and others have shown that high rates of MRD negativity and sustained MRD negativity are achieved with extensive quadruplet treatment approaches, it is time to re-evaluate the role of high-dose melphalan, especially considering recent findings of significantly increased mutational burden and detrimental long-term effects of genomic damage.[32-35]

In the near future, consequent implementation of T-cell engaging strategies in frontline treatment with CAR-T cell application replacing high-dose melphalan or use of bispecific antibodies in maintenance strategies will allow further treatment optimization and are expected to achieve unprecedented high MRD negativity and sustained MRD negativity rates. Results from randomized ongoing trials (eg, CARTITUDE-6 [ClinicalTrials.gov identifier: NCT05257083], MagnetisMM-7 [ClinicalTrials.gov identifier: NCT05317416])[36,37] are, therefore, eagerly awaited. To adequately evaluate these concepts for HR patients, particularly, and to better characterize tumor cell subsets, the HR disease definition should be aligned and may incorporate more advanced genomic profiling.

Our phase II, nonrandomized trial is limited by reliance on historical comparators or comparison with ongoing studies with a similar, but never completely equal, study design or population. Owing to the dismal outcomes of this HR population with standard regimens, a two-arm design with a

TABLE 2. AEs Until the End of Consolidation Separated by Study Arm (TE and TNE patients) and Grade (CTCAE, v5.0)

	TE Patients (n = 97), %		TNE Patients (n = 25), %	
AE	AE All Grades	AE Grade ≥3	AE All Grades	AE Grade ≥3
Patients with any AE	93.8	78.4	88	72
Hematologic				
Neutropenia	41.2	39.2	28	28
Leukopenia	25.8	24.7	4	4
Thrombocytopenia	27.8	26.8	20	16
Anemia	14.4	14.4	20	12
Nonhematologic				
Infection (total)	60.8	27.8	48	28
Gastrointestinal	19.6	9.3	28	4
Neuropathy	35.1	2.1	16	4
Cardiac	11.3	2.1	20	20
Hypertension	14.4	10.3	16	8
Renal	8.2	6.2	16	8
Infusion-related reaction	26.8	1	16	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TE, transplant-eligible; TNE, transplant-noneligible.

standard-of-care arm was ethically not justifiable. Furthermore, only patients who reached the start of maintenance could be included in the landmark analysis on sustained MRD negativity for ≥6 months, and patients who dropped out before (most commonly because of progressive disease) were not analyzed. Although a PFS benefit for patients being MRD-negative until the end of consolidation can be observed, significance is lacking because of short follow-up. Further investigation of sustained MRD negativity for ≥12 months requires a landmark beyond the start of maintenance and extended follow-up, which was not feasible for this report. The actual rate of ≥2 HRCAs is likely higher than reported because gain1q21 (three copies) was not considered an HRCA and thus not captured, and several patients with noncentral laboratory cytogenetic diagnostics were only tested for some HRCAs.

Taken together, there is now a strong body of evidence for HR disease, supporting use of the most effective multidrug treatment options in induction, followed by HDT-ASCT in TE patients, a prolonged consolidation, and a multidrug maintenance regimen. This approach, as shown in the CONCEPT trial with Isa-KRd, can lead to unprecedented rates of (sustained) MRD negativity and PFS duration in patients with HRNDMM.

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DATA SHARING STATEMENT

Any requests for individual data should be directed to the corresponding author; only reasonable requests with profound methodological approach will be considered, and approval of both the steering committee of the German-speaking Myeloma Multicenter Group and the Data Safety Monitoring Board must be obtained first.

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Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma

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Travel, Accommodations, Expenses: Amgen, Celgene, Bristol Myers Squibb, Janssen-Cilag, GlaxoSmithKline, Takeda, Menarini

No other potential conflicts of interest were reported.

APPENDIX 1. ADDITIONAL INFORMATION ON THE AMENDMENT OF THE PROTOCOL

The trial was originally designed to include 117 transplant-eligible (TE) and 36 transplant-noneligible (TNE) patients. Recruitment was completed in April 2020; the median follow-up at that time was 25 months. In an exploratory interim analysis on the first 50 patients, all 46 TE patients showed overall response and the four TNE patients had very good partial response (VGPR) or better (≥VGPR).[39] To strengthen the power of the secondary end point of progression-free survival (PFS), an extension of the 117 TE patients to a total of 210 TE patients was considered with a prolongation of the trial duration by 36 months. In addition, an extension of the sample size also enabled detailed subgroup analyses of populations with specific high-risk markers. The Protocol was therefore amended in 2021. The recalculation for the required number of TE patients to be enrolled was done as stated below.

Sample Size Calculation

Arm A: The median PFS in high-risk patients with standard therapy is considered to be (less than) 25 months.[40,41] A clinically relevant effect, which should be detected with a probability of at least 80%, is a prolongation of the median PFS compared with standard of care by 6 months to 31 months. A recruitment rate of 5-6 patients per month and a follow-up time of 36 months after inclusion of the last patient were assumed. A sample size of 189 evaluable patients with an expected number of 134 events allows rejection of the null hypothesis $S(t_0) \leq 0.5$ (S defining the survival distribution and $t_0 = 25$ months)—to be translated into median PFS ≤25 months—to detect a median PFS of 31 months with a power of 80%. Thus, a total of 189 evaluable patients are necessary for secondary efficacy analysis; with an assumed rate of 10% screening failure, a total of 210 TE patients need to be enrolled. To enable the evaluation of the primary end point as originally planned on the basis of 93 evaluable TE patients, a group sequential design with one efficacy interim analysis on the basis of 93 evaluable patients and a final analysis on 189 evaluable patients was adapted. The calculation was based on a one-sample log-rank test with a one-sided significance level of 5% assuming exponential survival times.[14] With respect to the primary end point, 189 patients provide a cumulative power of 93.8% to detect an increased minimum residual disease (MRD) negativity rate of 50%-62% at a cumulative one-sided significance level of 5%. For arm B, a sample size of 25 evaluable patients allows us to reject the null hypothesis of MRD negativity ≤30% on a one-sided $\alpha = 5\%$ with a power of 90% for a MRD negativity rate of 60%.

Because of the allocation to either TE or TNE, the two study arms can be seen as two separate phase II studies; therefore, the primary end point will be tested at an overall two-sided α level of 5% for each of the two study arms.

Additional Information on Treatment Schedule, Dosing, and Administration

Induction and consolidation cycles lasted 28 days, with isatuximab 10 mg/kg given intravenously (IV) once daily on days 1, 8, 15, and 22 during the first cycle and on days 1 and 15 on subsequent cycles; carfilzomib 20 mg/m^2 given IV once daily on days 1 and 2 and 36 mg/m^2 given IV once daily on days 8, 9, 15, and 16 of the first cycle and 36 mg/m^2 given once daily on days 1, 2, 8, 9, 15, and 16 of subsequent cycles (27 mg/m^2 throughout the consolidation cycle 1); lenalidomide 25 mg given orally once daily on days 1 through 21 (15 mg throughout consolidation cycle 1); and dexamethasone 40 mg given orally or IV once daily on days 1, 8, 15, and 22 (20 mg for patients age older than 75 years). Maintenance treatment cycles were 28 days and consisted of isatuximab 10 mg/kg given IV once daily on days 1 and 15, carfilzomib 70 mg/m^2 given IV once daily on days 1 and 15, and lenalidomide 15 mg given orally once daily on days 1 through 21.

Following a protocol amendment in 2021, carfilzomib dosing was changed to once weekly, with 56 mg/m^2 given IV once daily on days 1, 8, and 15 (20 mg/m^2 as the first dose of the induction cycle) of the induction and consolidation cycles.

Thromboembolic and herpes zoster prophylaxis were required throughout the trial; antibacterial prophylaxis was mandatory during the first two induction cycles and up to the investigator's discretion thereafter.

Hematopoietic stem-cell mobilization and collection, high-dose therapy with melphalan, and autologous stem-cell transplantation (ASCT) were not formally part of the trial but were done according to the local standard of care at the individual trial sites. Consolidation treatment was to begin 60 days after ASCT.

TABLE A1. Inclusion and Exclusion Criteria

Inclusion/Exclusion	Criteria
Inclusion criteria	Patients must satisfy the following criteria to be enrolled in the study: 1. Patients must have newly diagnosed, untreated, symptomatic (according to the revised C.R.A.B. criteria 2014), documented myeloma and have measurable disease (serum M protein ≥1 g/dL [for IgA ≥0.5 g/dL] or urine M protein ≥200 mg/24 h) or, in case of oligosecretory myeloma, have involved FLC level ≥10 mg/dL, provided the sFLC ratio is abnormal or, in case of nonsecretory myeloma, have >1 focal lesion measurable by MRI Patients must have high-risk myeloma, defined as follows: Presence of ≥1 of the following cytogenetic abnormalities (determined by FISH): del(17p) in ≥10% of purified cells t(4;14) >3 copies +1q21[a] t(14;16) ISS stage II or III (all patients) FISH analysis of external laboratories other than Heidelberg Engineering is accepted; a list of laboratories will be filed in the study central 2. Must be 18 years or older at the time of signing the informed consent form 3. Must be able to adhere to the study visit schedule and other protocol requirements in the investigator's opinion 4. WHO performance status 0-3 (WHO = 3 is allowed only if caused by MM and not by comorbid conditions) 5. Female patients of childbearing potential (1) must agree to refrain from becoming pregnant for 28 days before initiation of study drug, while on study drug, and for 150 days[a] after discontinuation from the study drug by using two reliable methods of contraception and must agree to regular pregnancy testing during this time frame A female of childbearing potential is a sexually mature woman who (1) has not undergone a hysterectomy or bilateral oophorectomy; (2) has not been naturally postmenopausal (amenorrhea after cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, who has had menses at any time in the preceding 24 consecutive months); or (3) has achieved menarche at some point 6. Female patients must agree to abstain from breastfeeding during study participation and for 150 days[b] after study drug discontinuation 7. Male patients must agree to use a latex condom during any sexual contact with women of childbearing potential while participating in the study and for 150 days[a] after discontinuation from this study, even if he has undergone a successful vasectomy 8. Male patients must also agree to refrain from donating semen or sperm while on treatment with any study drug and for 150 days[b] after discontinuation from this study treatment 9. All patients must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment 10. All patients must agree not to share medication 11. All participating patients must follow the requirements of the Lenalidomide Pregnancy Prevention Plan
Exclusion criteria	The presence of any of the following will exclude a patient from enrollment: 1. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to antiviral drugs. Known history of allergy to captisol (a cyclodextrin derivative used to solubilize carfilzomib), mannitol, sucrose, histidine (as base and hydrochloride salt), and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids and H2 blockers or that would prohibit further treatment with these agents 2. Patients with known systemic amyloidosis (except for AL amyloidosis of the skin or the bone marrow) 3. Administration of systemic chemotherapy, biological, immunotherapy, or any investigational agent (therapeutic or diagnostic) for MM, except bisphosphonate therapy. Emergency treatment with dexamethasone is allowed when the cumulative dexamethasone dose is ≤160 mg. It is allowed to include patients in the trial after 1 cycle (4 weeks) of any antimyeloma first-line treatment 4. Any of the following laboratory abnormalities: ANC <1,000/μL, unless related to myeloma Platelet count <30,000/μL (in case of platelets <50,000/μL and ≥30,000/μL myeloma bone marrow infiltration should be ≥50%) Corrected serum calcium >14 mg/dL (>3.5 mmol/L) or free ionized calcium >6.5 mg/dL (>1.6 mmol/L) Serum GOT/AST or SGPT/ALT >3.0 × ULN or serum total bilirubin >2.0 mg/dL if not because of hereditary abnormalities as Gilbert disease or hereditary hemolysis (note: if the mentioned limits for bilirubin or AST/ALT are exceeded but there is no significant hepatic dysfunction at investigator's discretion, the study office has to be consulted before inclusion) Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2, MDRD formula or CDK-EPI, or creatinine clearance <30 mL/min) 5. Active congestive heart failure (NYHA class III to IV), symptomatic cardiac ischemia, or conduction abnormalities uncontrolled by conventional intervention. Myocardial infarction within 4 months before study entry 6. Known HIV seropositive, hepatitis C infection, and/or hepatitis B (exception: patients with hepatitis B sAg and core antibody receiving and responding to antiviral therapy directed at hepatitis B are allowed). Patients with a history of hepatitis B infection have to be monitored repetitively during treatment. In case of signs of hepatitis B reactivation, antiviral treatment has to be initiated, and patients have to be referred to a specialist for treatment and monitoring of hepatitis infection 7. Acute active, uncontrolled infection 8. Significant neuropathy (grades 3-4 or grade 2 with pain according CTCAE V4.03) 9. Second malignancy within the past 5 years, except: Adequately treated basal cell or squamous cell skin cancer Carcinoma in situ of the cervix Prostate cancer Gleason Score ≤6 with stable PSA over the past 12 months Breast carcinoma in situ with full surgical resection Treated medullary or papillary thyroid cancer 10. Patients with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days before study entry 11. Major surgery within 4 weeks before cycle 1, day 1 (kyphoplasty is not considered major surgery); patients should have been fully recovered from any surgical-related toxicities 12. Female patients who are pregnant or lactating 13. Any other clinically significant medical disease or psychiatric condition that, in the investigator's opinion, may interfere with protocol adherence or a patient's ability to give informed consent 14. Participation in any other clinical trial (with the exclusion of observational, noninterventional studies)

Abbreviations: AL, amyloid light chain; ANC, absolute neutrophil count; CDK-EPI, chronic kidney disease epidemiology collaboration; C.R.A.B., calcium elevation, renal insufficiency, anemia, and bone abnormalities; CTCAE, common terminology criteria for adverse events; eGFR, estimated glomerular infiltration rate; FISH, fluorescence in situ hybridization; FLC, free light chain; GOT, glutamic oxaloacetic transaminase; IgA, immunoglobulin A; ISS, International Staging System; MDRD, modification of diet in renal disease; MM, multiple myeloma; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PSA, prostate-specific antigen; sFLC, serum free light chain; SGPT, glutamic-pyruvic transaminase; ULN, upper limit of normal.

[a]Following a protocol amendment in 2021, patients with three copies of 1q21 could also be included in the second cohort from 2021 onward, which is not part of this report.

[b]Twenty-eight days after the last dose of lenalidomide, 30 days after last dose of carfilzomib, and 150 days (5 months) after the last dose of isatuximab.

TABLE A2. Patient Characteristics of TE Patients Not Part of the Prespecified ITT-IA Population

Characteristic	TE Patients Not Part of the ITT-IA (n = 28)
Age, years, median (range)	59 (46-70)
Sex, No. (%)	
Female	12 (42.9)
Male	16 (57.1)
ECOG, No. (%)	
0-1	22 (78.6)
2-3	5 (17.9)
Missing	1 (3.6)
Disease isotype, No. (%)	
IgG	16 (57.1)
IgA	7 (25.0)
IgM	0 (0)
IgD	1 (3.6)
Light chain	4 (14.3)
Light chain, No. (%)	
Kappa	16 (57.1)
Lambda	12 (42.9)
Oligosecretory or nonsecretory disease, No. (%)	1 (3.6)
ISS stage, No. (%)	
II	18 (64.3)
III	10 (35.7)
R2-ISS, No. (%)	
I	5 (17.9)
II	6 (21.4)
III	10 (35.7)
IV	7 (25.0)
R2-ISS dichotomized, No. (%)	
I + II	11 (39.3)
III + IV	17 (60.7)
Cytogenetic aberration, No. (%)	
del(17p)	9 (32.1)
t(4;14)	14 (50.0)
t(14;16)	4 (14.3)
amp1q21	10 (35.7)
No. of HRCAs, No. (%)	
1 HRCA	20 (71.4)
≥2 HRCAs	8 (28.6)
Elevated LDH (>ULN), No. (%)	13 (46.4)
Therapy before enrollment, No. (%)	12 (46.2)
Plasma cell infiltration, % median (range)	59.5 (5.0-95.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HRCA, high-risk cytogenetic aberration; IgA, immunoglobulin A; IgD, immunoglobulin D; IgG, immunoglobulin G; IgM, immunoglobulin M; ISS, International Staging System; ITT-IA, intention-to-treat interim analysis; LDH, lactate dehydrogenase; TE, transplant eligible; R2-ISS, Second Revision of the International Staging System; ULN, upper limit of normal.

TABLE A3. Definition of Specific Terms by Preferred Term

Specific Term Label	Preferred Terms
Cardiac	Aortic valve incompetence, aortic valve stenosis, arrhythmia supraventricular, atrial fibrillation, cardiac failure, coronary artery disease, diastolic dysfunction, ejection fraction decreased, left ventricular dysfunction, mitral valve incompetence, myocarditis postinfection, tachycardia, tricuspid valve incompetence, ventricular tachycardia
Anemia	Anemia, hemoglobin decreased
Gastrointestinal (including diarrhea and vomiting)	Abdominal pain upper, clostridium difficile colitis, colitis, constipation, cytomegalovirus colitis, diarrhea, diarrhea hemorrhagic, dyspepsia, dysphagia, enteritis infectious, erosive esophagitis, esophageal candidiasis, gastritis, gastrointestinal disorder, gastrointestinal infection, nausea, oral candidiasis, oral herpes, procedural nausea, procedural vomiting, stomatitis, upper gastrointestinal hemorrhage, vomiting
Hypertension	Blood pressure increased, hypertension, hypertensive crisis
Infection	Abscess, arthritis bacterial, atypical pneumonia, bronchitis, bronchopulmonary aspergillosis, candida infection, COVID-19, cystitis, device-related infection, Escherichia infection, febrile bone marrow aplasia, febrile infection, febrile neutropenia, infection, influenza, influenza-like illness, neutropenic sepsis, parainfluenza virus infection, peritonsillar abscess, pharyngitis, pneumonia, influenzal pneumonia, pneumonia respiratory syncytial viral, pulmonary sepsis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sepsis, sinusitis, skin infection, staphylococcal sepsis, tooth abscess, tooth infection, upper respiratory tract infection, urinary tract infection, viral infection
Infusion-related reactions	Infusion-related reaction
Leukopenia	Leukopenia, WBC count decreased
Lymphopenia	Lymphopenia, lymphocyte count decreased
Neuropathy	Neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy
Neutropenia	Neutropenia, neutrophil count decreased
Renal	Acute kidney injury, renal impairment
Thrombocytopenia	Platelet count decreased, thrombocytopenia

TABLE A4. Multivariable Time-Varying Cox Regression Analysis to Evaluate the Prognostic Impact of the Achievement of MRD Negativity at Any Time on PFS

Covariate	Hazard Ratio	95% CI	*P*
MRD negative *v* non-negative	0.19	0.05 to 0.66	.009299
del(17p)			
Present *v* absent	1.25	0.52 to 2.99	.613215
t(14;16)			
Present *v* absent	1.42	0.56 to 3.57	.458972
amp1q21			
Present *v* absent	1.34	0.60 to 2.99	.478564
ISS stage III *v* II	1.2	0.52 to 2.76	.673104
LDH at baseline			
Normal *v* elevated >ULN	2.63	1.07 to 6.49	.035390

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase; MRD, minimal residual disease; PFS, progression-free survival; ULN, upper limit of normal.

TABLE A5. AEs Separated by Study Arm (TE and TNE patients) and Grades (CTCAE, vF5.0) Throughout the Whole Trial

Patients With AE of Specific Term	TE Patients (n = 97), %		TNE Patients (n = 25), %	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with any AE	97.9	82.5	88	80.0
Hematologic				
Neutropenia	53.6	50.5	28	28
Leukopenia	26.8	25.8	4	4
Thrombocytopenia	33.0	30.9	24	20
Anemia	15.5	15.5	28	12
Nonhematologic				
Infection (total)	75.3	33	56	32
Gastrointestinal	26.8	12.4	40	12
Neuropathy	46.4	3.1	24	4
Cardiac	14.4	2.1	24	24
Hypertension	18.6	13.4	20	12
Renal	9.3	7.2	16	8
Infusion-related reaction	28.9	1	16	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TE, transplant eligible; TNE, transplant noneligible.

TABLE A6. Listing of Infectious and Cardiac AEs Separated by Study Arm (TE and TNE patients) and Grades (CTCAE, vF5.0) Until End of Consolidation

Patients With AE of Specific Term	TE Patients (n = 97), %		TNE Patients (n = 25), %	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections				
Upper respiratory tract	15.5	3.1	8.0	4.0
Lower respiratory tract	14.4	8.2	16.0	16.0
Urinary tract	1.0	1.0	4.0	0
Neutropenic infection	11.3	6.7	4.0	4.0
Skin infection	2.1	1.0	0	0
Dental infection	0	0	8.0	0
Device-related infection	1.0	1.0	0	0
Not further specified or other	15.5	7.2	8.0	4.0
Cardiac				
Left ventricular dysfunction and cardiac failure	2.1	0	4.0	4.0
Valvulopathy	5.2	1.0	8.0	8.0
Supraventricular arrhythmia	0	0	4.0	4.0
Ventricular arrhythmia	0	0	4.0	4.0
Coronary artery disease	1.0	0	0	0
Other	3.1	1.0	0	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TE, transplant eligible; TNE, transplant noneligible.

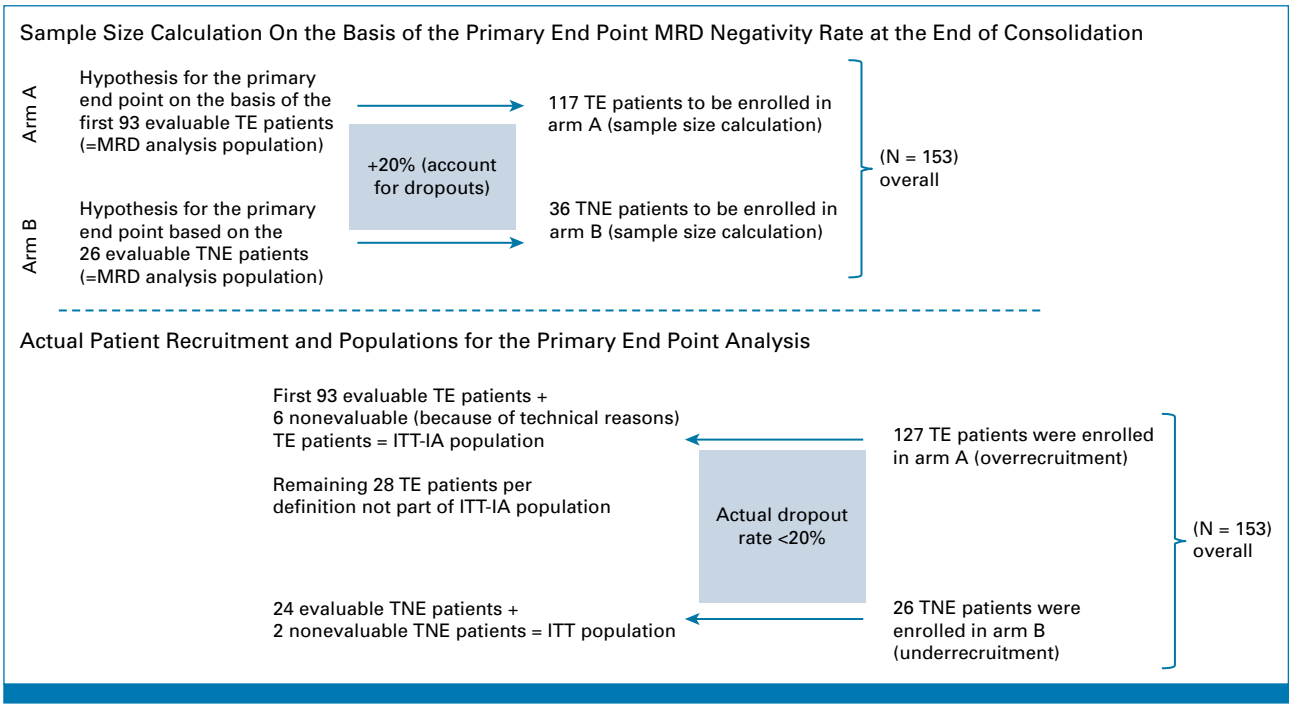

FIG A1. Depiction of analysis populations. IA, interim analysis; ITT, intention-to-treat; MRD, minimum residual disease; TE, transplant-eligible; TNE, transplant-noneligible.

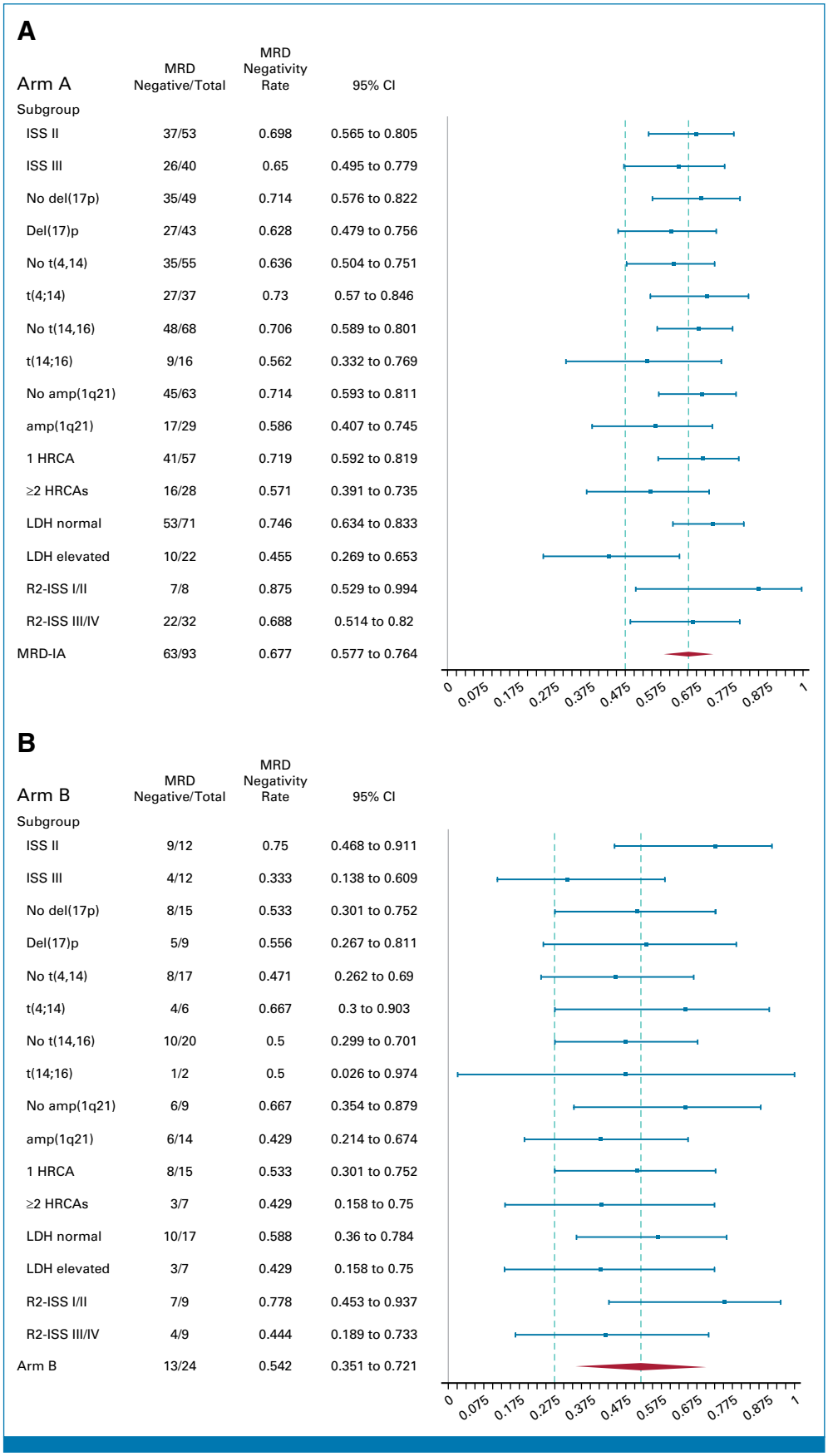

FIG A2. Forest plots displaying achievement of MRD negativity end point according to specific subsets of transplant-eligible (A) and transplant-noneligible (B) patients. HRCA, high-risk (continued on following page)

FIG A2. (Continued). cytogenic aberration; ISS, International Staging System; LDH, lactate dehydrogenase; MRD, minimal residual disease; R2-ISS, Second Revision of the International Staging System.

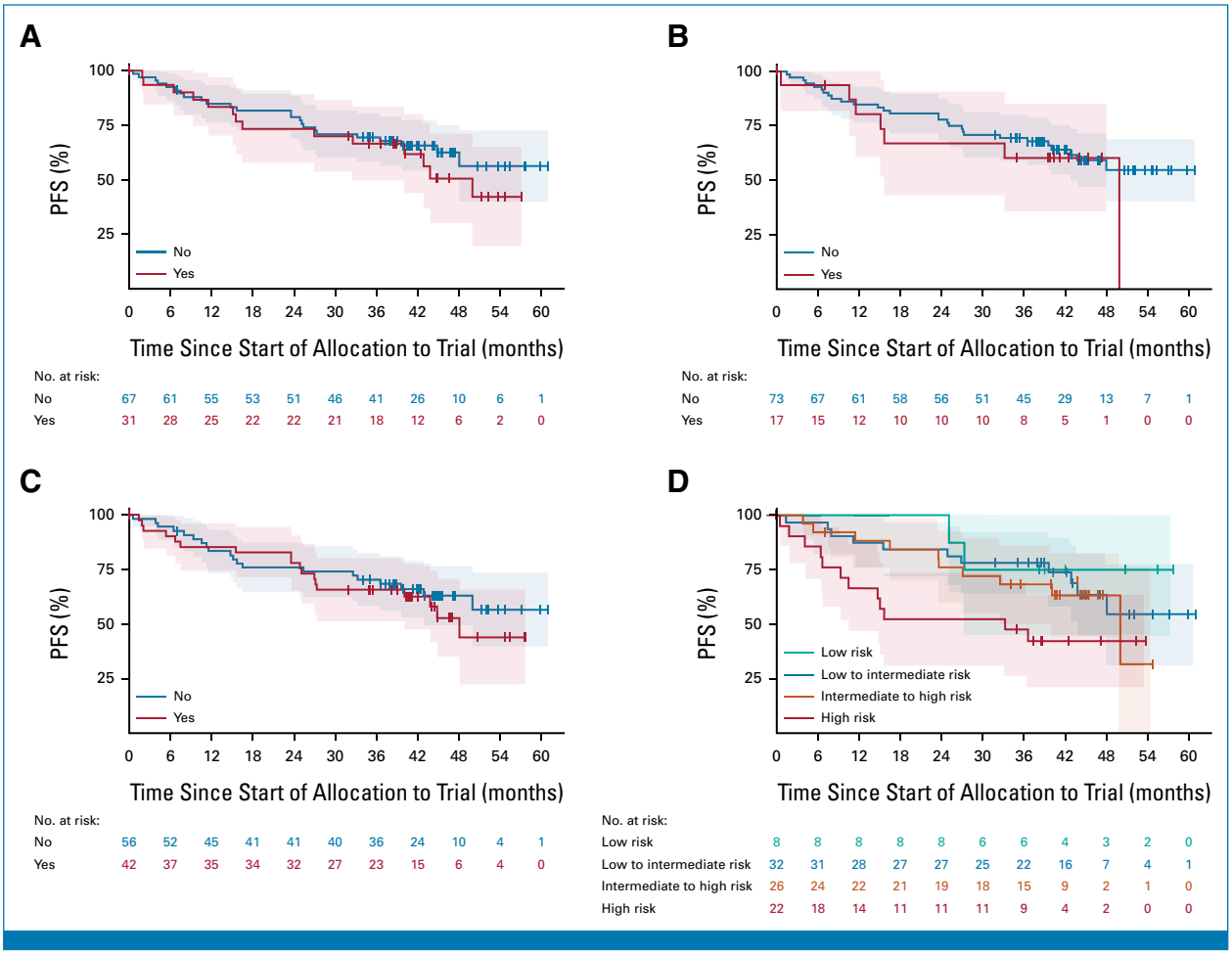

FIG A3. PFS in transplant-eligible patients according to the presence (red) or absence (blue) of (A) amplification of 1q21, (B) t(14;16), (C) t(4;14), or (D) according to R2-ISS. PFS, progression-free survival; R2-ISS, Second Revision of the International Staging System.