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Lenalidomide based triplets in relapsed/refractory multiple myeloma: analysis of the Czech Myeloma Group

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Abstract

Despite significant advancements in therapy of multiple myeloma (MM) over the past 20 years, most patients experience relapse, necessitating new treatment approaches. This study aims to compare the real-world effectiveness of lenalidomide (LEN)-based triplet therapies, specifically daratumumab (DRD), carfilzomib (KRD), and ixazomib (IRD), in relapsed/refractory multiple myeloma (RRMM).

A retrospective registry-based study analyzed 538 RRMM patients undergoing therapy for their first to third relapse. The primary endpoints were overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), with a matching-adjusted indirect comparisons (MAIC) employed to address cohort differences.

ORR was highest for DRD at 91.4%, followed by KRD (89.6%) and IRD cohorts (Early-IRD: 79.6%, Late-IRD: 70.8%). Median PFS for DRD was greater at 23.64 months compared to KRD (16.52 months) and IRD groups (Early-IRD: 19.97 months, Late-IRD: 11.57 months). The MAIC confirmed better outcomes for the DRD regimen. High-risk features were not overcome by any of the LEN-based regimens.

The findings underscore the superior efficacy of DRD in achieving sustained responses in RRMM patients. The composition of the cohort is a crucial factor, extending beyond selection criteria. This study highlights the importance of real-world evidence in assessing treatment modalities in clinical settings.

Keywords Multiple myeloma, Relapsed/refractory, Lenalidomide triplets, Risk groups

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Introduction

Multiple myeloma (MM) is a clonal B-cell neoplasm characterized by the proliferation and accumulation of terminally differentiated clonal plasma cells (≥10%) in the bone marrow or biopsy-proven plasmacytoma, accompanied by myeloma-defining events (MDE) and the presence of monoclonal immunoglobulin (MIG, M-protein) in the blood and/or urine [1]. The prognosis of MM has improved significantly over the last 20 years with the introduction of novel drugs, including proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and monoclonal antibodies (MoAb). Despite these advances, most patients eventually relapse and become relapsed or relapsed/refractory (RRMM), requiring further treatment.

Currently, the standard therapeutic recommendations for RRMM patients encompass various treatment modalities, dominantly relying on data from clinical trials [2, 3]. The most effective regimens include lenalidomide (LEN) plus dexamethasone-based triplets, such as KRD (with carfilzomib), DRD (with daratumumab), IRD (with ixazomib), and EloRD (with elotuzumab). Based on the results of phase III clinical trials, these regimens have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for RRMM within relapses 1–3 [4–7].

Although several network meta-analyses have compared individual regimens, there have been no head-to-head clinical trials thus far [8–10]. These comparisons show better outcomes with DRD, while also acknowledging cohort heterogeneity. However, in routine practice, treatment outcomes are generally worse than those observed in clinical trials, as many patients would not meet the eligibility criteria for such trials. Real-world evidence (RWE) data comparing LEN-based triplets in RRMM have demonstrated a gap between clinical trials and RWE, highlighting the limited generalizability of clinical trials and the need for further RWE analyses [11, 12].

Given the specific conditions for the treatment of RRMM in the Czech Republic, we decided to conduct a retrospective study to compare LEN-based triplets in routine clinical practice.

Patients and methods

Study design

We conducted a registry-based study focused on the treatment of relapsed/refractory multiple myeloma (RRMM) patients undergoing therapy in their first to third relapse in routine clinical practice. The study excluded patients treated with VRD (bortezomib, lenalidomide, dexamethasone) and EloRD (elotuzumab, lenalidomide, dexamethasone) due to insufficient numbers for proper statistical analysis (<30 patients). The assessment followed a pre-specified statistical analysis plan.

Inclusion criteria

Patients included in the study met the following criteria:

1. Diagnosed with RRMM and registered with the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group.
2. Experiencing their first to third relapse according to International Myeloma Working Group (IMWG) criteria.
3. Undergoing therapy with one of the following regimens: DRD (daratumumab, lenalidomide, dexamethasone), KRD (carfilzomib, lenalidomide, dexamethasone), or IRD (ixazomib, lenalidomide, dexamethasone).

Exclusion criteria

Patients were excluded if they:

1. Underwent repeated therapy with the same RD-based regimen.
2. Participated in a clinical trial.
3. Switched treatment for reasons other than disease progression or toxicity.
4. Initiated treatment after June 30, 2021.*
5. Had a follow-up period from the start of the selected regimen to progression or death shorter than six months.*
6. Completed fewer than two cycles of the selected regimen.*

*These criteria ensured sufficient follow-up for statistical analysis.

We did not exclude patients with inferior performance status, or those pre-treated or refractory to lenalidomide and bortezomib, who would otherwise be ineligible for clinical trials.

Specific conditions for each regimen

Therapy availability and reimbursement in the Czech Republic influenced treatment conditions:

- *Ixazomib (IRD regimen)*: Available via a Named Patient Program (NPP) from 2016–2018, before other LEN-based triplets were reimbursed. Post-2019, ixazomib was reimbursed, but mostly used for patients ineligible for DRD or KRD, leading to the creation of two separate IRD cohorts: early IRD (E-IRD) for NPP

patients, and late IRD (L-IRD) for those treated post-2019.

- *Carfilzomib*: Became available in 2018. Initially, no other LEN-based triplets were available, and competing clinical trials were ongoing.
- *Daratumumab (DRD)*: Available since late 2019 and became the first choice for RRMM treatment based on clinical trial data.

Cohort definition and endpoints

After applying inclusion and exclusion criteria, 538 patients were analyzed across four cohorts: DRD (224 patients), KRD (143 patients), E-IRD (104 patients), and L-IRD (67 patients). Demographic data and basic patient and disease characteristics are summarized in Table 1 and in Supplementary material.

Primary Endpoints: Overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Secondary Endpoints: Very good partial response (VGPR) rate, PFS in specified prognostic subgroups, and the rate of adverse events. We did not choose the rate of complete responses (CR) or minimal residual disease (MRD) negativity as secondary endpoints due to the treatment until progression and limited bone marrow data availability for CR and MRD assessment.

Statistical considerations

Due to the differences between the individual groups (DRD, KRD, E-IRD, L-IRD), a matching-adjusted indirect comparisons (MAIC) analysis was applied. This approach follows the methodologies outlined by Signorovitch et al. (2010) and Richter et al. (2023) [13, 14]. The analysis was performed using the R package `maic` (Young R., 2022) [15].

The following variables were matched:

1. Age
2. Line of treatment
3. ISS stage
4. Characteristics of therapy: lenalidomide pretreatment
5. Immunomodulatory drugs (IMiD)—refractory
6. Cytogenetics – risk groups

Table 1 Basic characteristics at treatment initiation

	Total *N* = 538	**DRd** *N* = 224	**E-IRd** *N* = 104	**L-IRd** *N* = 67	**KRd** *N* = 143	***p*-value**[1]
Sex						0.836
Man	297 (55.2%)	125 (55.8%)	60 (57.7%)	34 (50.7%)	78 (54.5%)	
Woman	241 (44.8%)	99 (44.2%)	44 (42.3%)	33 (49.3%)	65 (45.5%)	
Age [years]						**< 0.001**
< 65	246 (45.7%)	108 (48.2%)	39 (37.5%)	21 (31.3%)	78 (54.5%)	
65–75	252 (46.8%)	99 (44.2%)	59 (56.7%)	34 (50.7%)	60 (42.0%)	
> 75	40 (7.4%)	17 (7.6%)	6 (5.8%)	12 (17.9%)	5 (3.5%)	
Age						**< 0.001**
N	538	224	104	67	143	
Median (5%–95%)	65.9 (45.3–77.9)	65.5 (45.0–77.8)	67.2 (45.9–76.3)	69.9 (53.1–79.9)	64.4 (46.6–75.4)	
Performance status [ECOG]						**0.012**
PS 0–1	463 (86.7%)	196 (87.9%)	86 (83.5%)	51 (76.1%)	130 (92.2%)	
PS 2	62 (11.6%)	25 (11.2%)	16 (15.5%)	12 (17.9%)	9 (6.4%)	
PS 3–4	9 (1.7%)	2 (0.9%)	1 (1.0%)	4 (6.0%)	2 (1.4%)	
Unknown	4	1	1	0	2	
ISS stage						**0.034**
Stage 1	208 (47.9%)	89 (48.4%)	35 (42.2%)	18 (37.5%)	66 (55.5%)	
Stage 2	122 (28.1%)	41 (22.3%)	29 (34.9%)	18 (37.5%)	34 (28.6%)	
Stage 3	104 (24.0%)	54 (29.3%)	19 (22.9%)	12 (25.0%)	19 (16.0%)	
Unknown	104	40	21	19	24	
Extraosseous disease						0.324
No	155 (63.5%)	79 (67.5%)	26 (65.0%)	13 (68.4%)	37 (54.4%)	
Yes	89 (36.5%)	38 (32.5%)	14 (35.0%)	6 (31.6%)	31 (45.6%)	
Unknown	294	107	64	48	75	

[1] Pearson's Chi-squared test; Kruskal–Wallis rank sum test; Fisher's exact test

7. Performance status (ECOG)
8. Extraosseous disease
9. Characteristics of therapy: transplantation
10. Sex

These variables were selected by the researcher, and their significance was determined through statistical assessment. Variables with the strongest representation and significant differences were adjusted to account for possible bias, as shown in Supplementary Tables 1 and 2. All variables were matched to summary statistics of the entire group (DRD + KRD + E-IRD + L-IRD) for each individual cohort. Due to the low representation of Extraosseous disease in individual cohorts, this variable could not be matched in the MAIC analysis.

Each patient in an individual cohort was assigned a weight to ensure that the summary statistics of the cohort matched those of the entire group. In this re-weighted cohort, a weight > 1 indicates that a patient carries more weight than in the original data, while a weight < 1 indicates that a patient carries less weight.

Matching was conducted in a stepwise manner based on the significance of the variables. Variables were added to the algorithm gradually, starting with one variable, then two, and so on.

The MAIC matching algorithm required non-binary categorical variables (ISS stage and Performance status [ECOG]) to be divided into two subsequent binary variables to ensure the correct ratio. The variable "Line of treatment" was considered as a continuous variable for the MAIC matching algorithm.

Risk group analysis

Patients in individual cohorts were divided based on selected risk categories, and PFS curves were calculated for these subgroups: del(17p13), t(4;14), t(14;16), gain(1q21), high-risk cytogenetics – any of del(17p13), t(4;14) or t(14;16), ISS stage, disease status (relapsed, relapsed/refractory, primary refractory), extraosseous disease. High-risk cytogenetics was defined as per the recommendations in Revised International Staging System (R-ISS) and Second Revision of the International Staging System (R2-ISS) [16, 17].

PFS curves were created only for groups with more than 13 patients.

Results

The median follow-up was: DRD: 16.2 months (4.5–29.7), KRD: 24.6 months (5.3–48.2), E-IRD: 36.2 months (4.6–68.0), and L-IRD: 17.2 months (2.0–33.1).

Response rates

The overall response rates (PR or better) for individual treatment regimens were as follows: DRD 91.4%, KRD 89.6%, E-IRD 79.6%, L-IRD 70.8%, $p < 0.001$. VGPR or better was reached in: DRD 67.3%, KRD 62.3%, E-IRD 40.8%, L-IRD 25.0%. Detailed treatment responses are shown in Table 2.

Table 2 Response rates

	Total *N* = 538	DRd *N* = 224	E-IRd *N* = 104	L-IRd *N* = 67	KRd *N* = 143	*p*-value[1]
Maximal treatment response						
sCR, CR	38 (8.1%)	12 (6.5%)	12 (12.2%)	–	14 (10.4%)	
VGPR	223 (47.8%)	113 (60.8%)	28 (28.6%)	12 (25.0%)	70 (51.9%)	
PR	142 (30.4%)	45 (24.2%)	38 (38.8%)	22 (45.8%)	37 (27.4%)	
MR	31 (6.6%)	6 (3.2%)	10 (10.2%)	7 (14.6%)	8 (5.9%)	
SD	21 (4.5%)	8 (4.3%)	7 (7.1%)	4 (8.3%)	2 (1.5%)	
PD	12 (2.6%)	2 (1.1%)	3 (3.1%)	3 (6.2%)	4 (3.0%)	
Unknown	71	38	6	19	8	
Overall Response Rate (PR or better)						**< 0.001**
No	64 (13.7%)	16 (8.6%)	20 (20.4%)	14 (29.2%)	14 (10.4%)	
Yes	403 (86.3%)	170 (91.4%)	78 (79.6%)	34 (70.8%)	121 (89.6%)	
Unknown	71	38	6	19	8	
Clinical Benefit Rate (MR or better)						0.053
No	33 (7.1%)	10 (5.4%)	10 (10.2%)	7 (14.6%)	6 (4.4%)	
Yes	434 (92.9%)	176 (94.6%)	88 (89.8%)	41 (85.4%)	129 (95.6%)	
Unknown	71	38	6	19	8	

[1] Pearson's Chi-squared test; Fisher's exact test

Progression-Free Survival (PFS)

The median progression-free survival (PFS) for each cohort was as follows:: DRD 23.64 months (17.02–NA), KRD 16.52 months (12.62–23.54), E-IRD 19.97 months (13.41–26.62), L-IRD 11.57 months (8.95–13.48), $p < 0.001$, Fig. 1. Median PFS in the first relapse: DRD not reached, KRD 18.85 months (13.08–29.84), E-IRD 27.15 months (15.15–35.11), L-IRD 11.57 months (8.75–19.51), $p = 0.004$.

Overall Survival (OS)

Median OS was reached only in the L-IRD cohort: 25.57 months (20.39-NA). Therefore, we report the survival rates after 1 year and 2 years of treatment. 12-month OS was: DRD 80.9%, KRD 81.8%, E-IRD 80.8%, L-IRD 72.3%. 24-month OS: DRD 73.4%, KRD 61.2%, E-IRD 72.0%, L-IRD 57.1%. 36-month OS: DRD 62.5%, KRD 53.0%, E-IRD 61.7%, L-IRD 42.6% ($p = 0.06$).

MAIC analysis

MAIC analysis accounted for up to four selected variables. Matching for a higher number of variables reduced the effective sample size (ESS), precluding valid statistical analysis. After matching four variables, no statistically significant difference remained within the unmatched variables. Matching for age only: Median PFS – DRD 23.64 months, KRD 17.25 months, E-IRD 19.97 months, L-IRD 9.64 months ($p = 0.001$). Matching for age, line of treatment, and ISS: Median PFS – DRD 20.69 months, KRD 15.48 months, E-IRD 15.8 months, L-IRD 9.64 months ($p = 0.098$). Matching for age, line of treatment, lenalidomide, and IMiD pretreatment: Median PFS – DRD 22.72 months, KRD 16.39 months, E-IRD 19.97 months, L-IRD 9.64 months ($p = 0.002$). Matching for age, line of treatment, lenalidomide pretreatment, and cytogenetic risk: Median PFS – DRD 11.9 months, KRD 17.5 months, E-IRD 13.4 months, L-IRD 9.6 months ($p = 0.055$).

Risk group analysis

The presence of del(17p13) led to significantly inferior results in PFS for the DRD regimen, with a median of 5.87 months compared to 20.69 months in those without the deletion ($p < 0.001$). In contrast, the differences in PFS were not significant for the KRD, E-IRD, and L-IRD regimens, Fig. 2.

Similarly, the presence of t(4;14) resulted in significantly inferior median PFS for both the DRD regimen (9.05 vs 21.57 months, $p < 0.001$) and the KRD regimen (12.62 vs 17.90 months, $p = 0.03$). However, the differences were insignificant for the L-IRD regimen (9.64 vs 10.79 months, $p = 0.403$). The number of t(4;14) patients

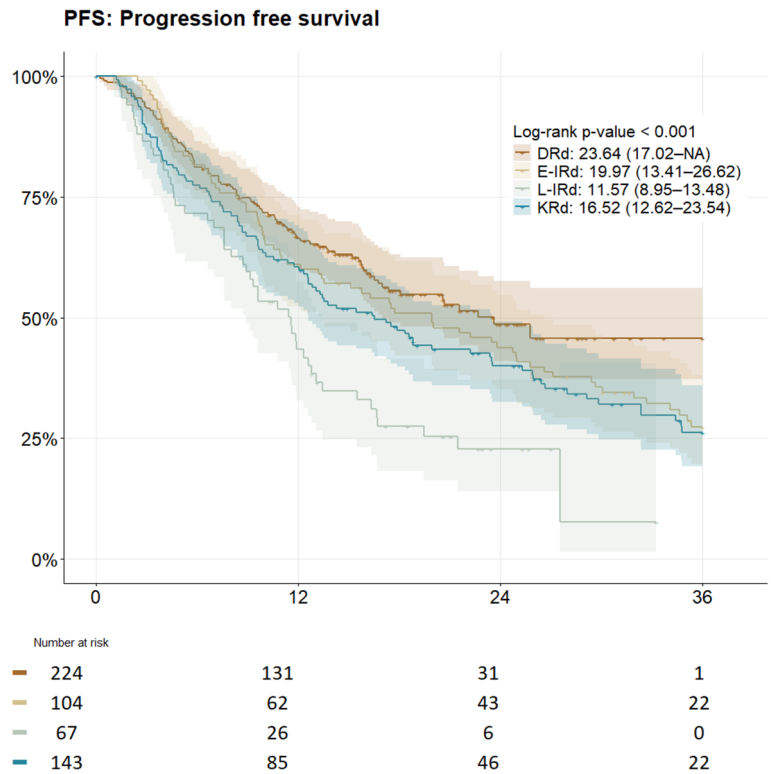

Fig. 1 Progression free survival in lenalidomide based triplets

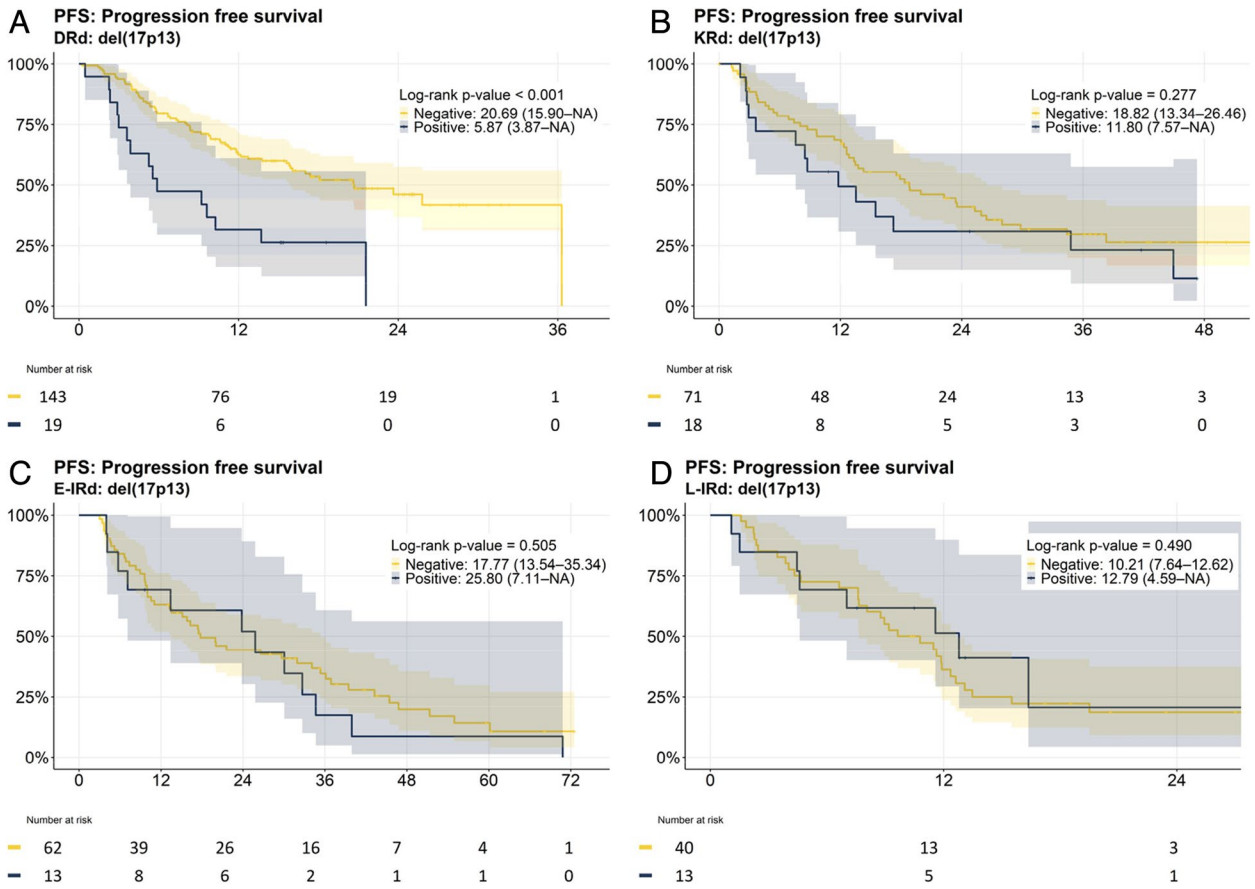

Fig. 2 Progression free survival in patients treated by RD triplets by the presence of del(17p13)

A – DRD regimen (daratumumab, lenalidomide, dexamethasone). **B** – KRD regimen (carfilzomib, lenalidomide, dexamethasone). **C** – E-IRD regimen („early" ixazomib, lenalidomide, dexamethasone). **D** – L-IRD regimen („late" ixazomib, lenalidomide, dexamethasone)

in the E-IRD cohort was below the threshold for statistical analysis, as was the number of patients with t(14;16) in each cohort.

High-risk cytogenetics, including del(17p13), t(4;14), and t(14;16), significantly impacted the outcomes for the DRD regimen (median PFS: 8.36 vs 25.80 months, $p<0.001$). The KRD regimen showed borderline significance (median PFS: 13.54 vs 23.41 months, $p=0.049$), while the trends in both E-IRD (median PFS: 13.41 vs 21.61 months, $p=0.441$) and L-IRD (median PFS: 11.57 vs 9.18 months, $p=0.785$) groups were insignificant, Fig. 3.

The presence of 1q21 also led to inferior median PFS in all regimens: DRD (11.87 vs 36.30 months, $p=0.002$), KRD (12.62 vs 23.54 months, $p=0.01$), and E-IRD (13.25 vs 30.07 months, $p=0.003$). The L-IRD regimen showed insignificant results (median PFS: 9.64 vs 11.48 months, $p=0.345$), Fig. 4.

Inferior median PFS was observed in patients with extraosseous disease in the DRD (NA vs 36.3 months, 12-month PFS 51.0% vs 84.7%, $p=0.038$), KRD (5.15 vs 23.41 months, $p<0.001$), and E-IRD (8.66 vs 29.67 months, $p=0.002$) cohorts, Fig. 5. The number of patients with extraosseous disease in the L-IRD cohort was below the threshold for statistical analysis.

The International Staging System (ISS) at the time of MM progression showed a trend towards worse outcomes in advanced ISS groups, but the results were insignificant in all cohorts: DRD (median PFS: ISS 1—not reached vs ISS 2—20.69 vs ISS 3—16.07 months, $p=0.2$), KRD (median PFS: ISS 1—17.25 vs ISS 2—13.77 vs ISS 3—16.52 months, $p=0.665$), and E-IRD (median PFS: ISS 1—24.95 vs ISS 2—13.54 vs ISS 3—17.77 months, $p=0.166$).

Significantly worse outcomes were observed in relapsed/refractory (RR) and primary refractory patients compared to those with relapsed MM only.

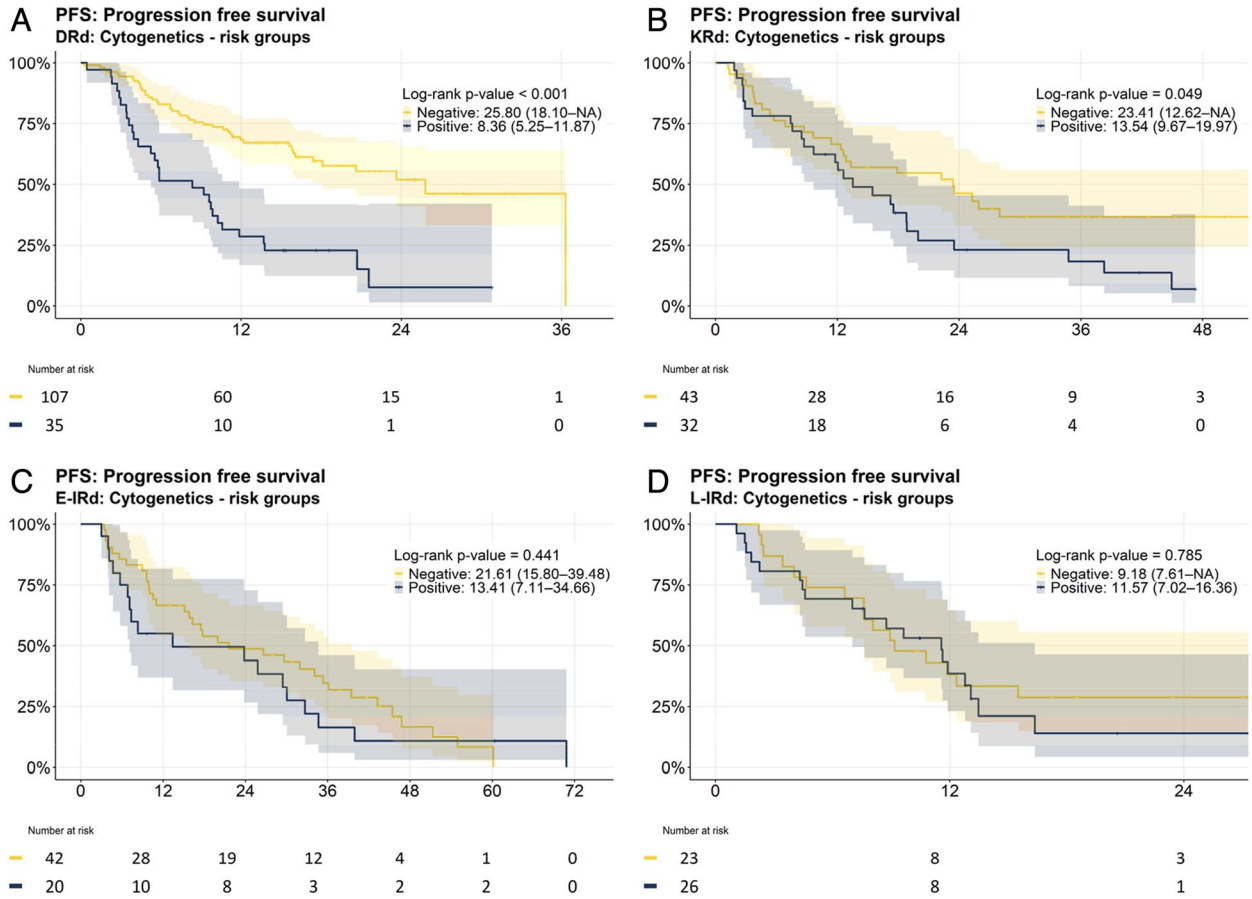

Fig. 3 Progression free survival in patients treated by RD triplets by the presence of high- risk cytogenetics

A – DRD regimen (daratumumab, lenalidomide, dexamethasone). **B** – KRD regimen (carfilzomib, lenalidomide, dexamethasone). **C** – E-IRD regimen („early" ixazomib, lenalidomide, dexamethasone). **D** – L-IRD regimen („late" ixazomib, lenalidomide, dexamethasone)

Due to low patient counts in RR and primary refractory groups, detailed data is not shown.

Toxicities

Toxicities are in accord with previously reported data, the outcomes are summarized in Supplementary files. The majority of grade ≥ 3 toxicities included hematological toxicities (anemia, neutropenia, thrombocytopenia) followed by infections. Treatment-specific adverse events of grade ≥ 3 such as neuropathy, cardiotoxicity, venous thromboembolism, rash, diarrhea, nausea, and anorexia were all below 5%. No new safety alerts were recorded within the RRMM patient group.

Treatment withdrawal due to toxicity did not significantly differ among the cohorts, with the lowest rate in the E-IRD group (4.3%) and the highest rate in the L-IRD group (11.5%).

Discussion

Until the introduction of lenalidomide (LEN) maintenance in frontline settings (both for transplant-eligible and ineligible patients), lenalidomide-based triplets were the standard of care for patients with relapsed/refractory multiple myeloma (RRMM) [18]. Even now, LEN-based triplets remain a preferred option for some patients who progress on alternative regimens or after a longer treatment-free period, as recommended by the European Society of Medical Oncology (ESMO) and International Myeloma Working Group (IMWG) guidelines [2, 3]. Although there has been no randomized clinical trial directly comparing different LEN-based triplets, registration clinical trials have shown that these regimens offer significantly better response rates and survival outcomes than lenalidomide and dexamethasone alone [4–7, 19, 20].

Several network meta-analyses have favored the DRD regimen (with daratumumab) over other LEN-based

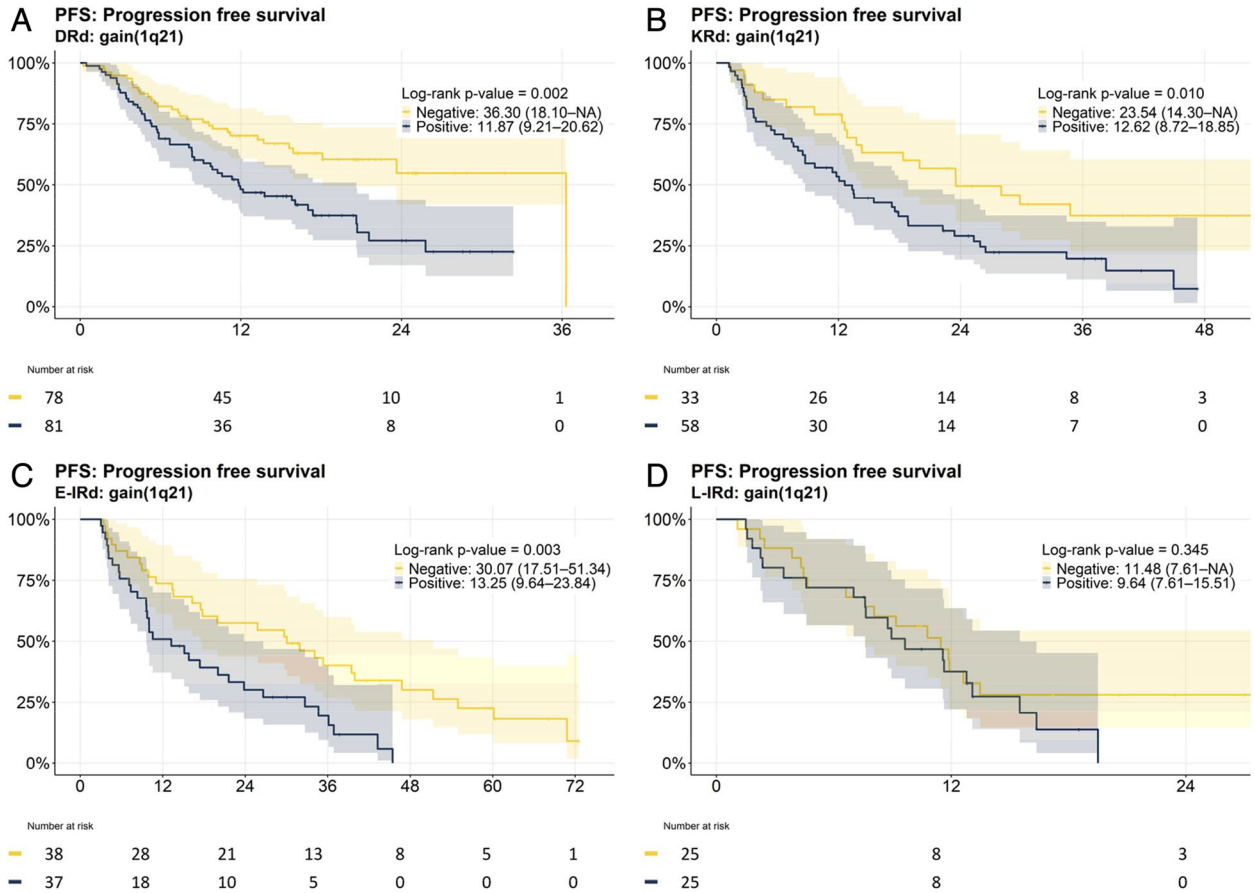

Fig. 4 Progression free survival in patients treated by RD triplets by the presence of gain/amp 1q21

A – DRD regimen (daratumumab, lenalidomide, dexamethasone). B – KRD regimen (carfilzomib, lenalidomide, dexamethasone). **C** – E-IRD regimen („early " ixazomib, lenalidomide, dexamethasone). **D** – L-IRD regimen („late " ixazomib, lenalidomide, dexamethasone)

combinations [8–11]. However, these analyses did not account for patients outside clinical trials. In routine practice, or the "real world" (RW) population, treatment outcomes typically do not match those reported from clinical trials due to substantial heterogeneity among patients, including those who would not be eligible for clinical trials. Despite this, RW data still show reasonable response rates and survival outcomes for LEN-based therapies [21–26].

Clinical trials and meta-analyses are considered the strongest sources of evidence for decision-making. RW data play an important, though complementary, role due to their limitations, such as retrospective observation bias, lack of randomization, and absence of placebo control. Another potential source of bias is the constitution of the cohort itself, apart from the selection criteria. For instance, our patients treated with ixazomib within the E-IRD or L-IRD cohorts illustrate this point. The E-IRD cohort included a general RRMM population, and the outcomes were similar to those reported in clinical trials [6, 26]. However, applying the same selection criteria to a new population a few years later resulted in a different cohort (L-IRD), with slightly older patients, worse performance status, more advanced ISS, and high-risk cytogenetics, leading to significantly worse outcomes.

To address these cohort differences, we performed a matching-adjusted indirect comparisons (MAIC) analysis to account for imbalances. The MAIC analysis confirmed better outcomes for the DRD regimen, although the differences among the cohorts were not as pronounced. MAIC results are useful for comparing groups but not for assessing survival measures directly, as each variable is weighted based on its importance. High-risk prognostic factors, such as higher age, line of treatment, and ISS stage, significantly impact the results. Notably, cytogenetic risk significantly decreases median progression-free survival (PFS) across all cohorts, with the

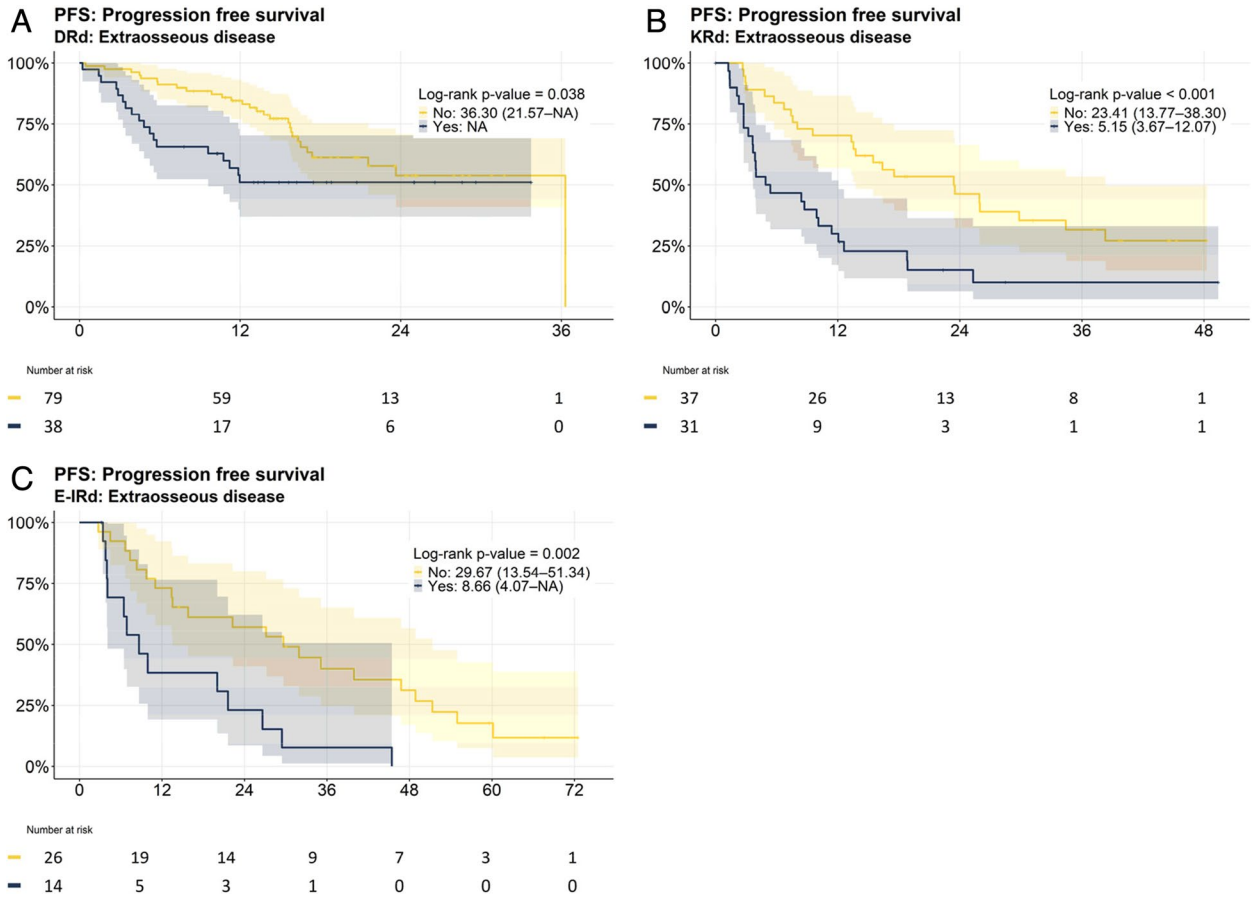

Fig. 5 Progression free survival in patients treated by RD triplets by the presence of extraosseous disease

A – DRD regimen (daratumumab, lenalidomide, dexamethasone). **B** – KRD regimen (carfilzomib, lenalidomide, dexamethasone). **C** – E-IRD regimen („early" ixazomib, lenalidomide, dexamethasone). L-IRD regimen not shown (number of patients with presence of extraosseous disease was below the selected limit)

deepest decrease seen in the DRD regimen, which is generally not recommended for patients with unfavorable cytogenetics [27]. Outcomes for patients with high-risk cytogenetics were slightly better when treated with KRD and E-IRD but the overal impact of adverse cytogenetics was consistent with previously published data [16, 17].

High-risk features were not overcome by any of the LEN-based regimens. Nonetheless, RW analysis suggested slightly better outcomes for patients with high-risk cytogenetics treated with combinations including proteasome inhibitors (PI), such as KRD or IRD, rather than PI-free regimens.The prognostic impact of gain/amp 1q21 and its association with poor outcomes across several therapeutic approaches has been well established for a long time [28, 29]. The presence of gain/amp 1q21, recognized as a poor prognostic factor in the R2-ISS staging, confirmed its adverse impact on all groups, including DRD, KRD, and E-IRD [17]. In our analysis, patients without 1q21 impairment had median PFS resembling those in clinical trials, suggesting the relevance of this prognosticator. Other factors outweighed the impact of 1q21 in the L-IRD cohort. The presence of extraosseous disease (both extramedullary and paramedullary) showed similar inferior outcomes across all treatment regimens, which is in accord with recent knowledge as well as our previously published data on limited efficacy of selected regimens [26, 30].

As LEN-based triplet efficacy decreases with advanced disease and may be biased by prior treatment, we also performed a comparative analysis focused on the first relapse, showing outcomes similar to those recently reported by Mangiacavalli et al. The analysis indicated better results for the DRD regimen (mPFS in our cohort not reached vs. 29.8 months reported by Mangiacavalli) compared to KRD (mPFS 18.85 months vs. 22.5 months), with E-IRD outcomes (not reported by Mangiacavalli)

surprisingly close to DRD, demonstrating the effectiveness of this all-oral triplet (mPFS 27.15 months) [12].

We acknowledge the limitations of our study, including the lack of randomization and potential selection bias in the patient cohorts. Additionally, the statistical methods used, including the MAIC analysis, may have introduced bias while attempting to match the different cohorts. Despite these statistical adjustments, our study may still carry biases inherent to all real-world analyses. However, since most patients in real-world settings would not be eligible for clinical trials, our analysis provides a valuable complementary source of information for routine practice.

In the real world, patient populations differ significantly from those in clinical trials. Factors such as demographic and tumor characteristics, high-risk features, performance status, and frailty affect outcomes and are not easily detected through standard selection criteria. Patients outside clinical trials typically receive less intensive therapy for shorter durations, not only due to adverse events or progression but also due to minor complaints leading to treatment discontinuation. Motivation to remain on treatment decreases more rapidly outside clinical trials.

The composition of the cohort is a crucial factor, extending beyond selection criteria. Competing treatment modalities significantly impact the measures of analyzed cohorts, as seen with E-IRD and L-IRD. Statistical adjustments are necessary to account for group imbalances in comparing heterogeneous cohorts.

We conclude that LEN-based triplets are effective in the RW setting. Most patients in routine practice would not qualify for clinical trials, a key factor for differing RW results. Despite identical selection criteria, final outcomes can vary significantly depending on multiple variables, particularly those involved in cohort constitution. MAIC analysis showed better outcomes for DRD compared to other LEN-based triplets, though not for patients with high-risk cytogenetics, where PI combinations had more favorable results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14087-y.

Supplementary Material 1.

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Patient consent statement
All patients gave written informed consent and the research was carried out in accordance with the Helsinki declaration.

Authors' contributions
JM wrote the manuscript, JM, VM and RH were responsible for study conception and design; JM, LP, VL, TJ, JS, AJ, JR, PP, MS, TP, PK, TP, FS, IS, PJ, VC, VM and RH. collected the data, provided study materials and patients; JM, JR, TJ and RH analyzed and interpreted the data; All co-authors critically revised and approved the paper.

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Data availability
The data of each patient were blinded and recorded under a unique code into the Registry of Monoclonal Gammopathies (RMG), a large multicenter database collecting data of MM patients within the Central Europe.
The datasets generated and/or analysed during the current study are not publicly available as local restrictions apply to the availability but are available from the corresponding author on reasonable request and with permission of all cooperating centres.

Declarations

Ethics approval and consent to participate
The ethical committees of participating Institutions approved the informed consent and inclusion of patients into the Registry of Monoclonal Gammopathies. The overal study was approved by the Ethics comittee of University Hospital Olomouc:
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Consent for publication
Not applicable.

Competing interests
JM had consultancy and received honoraria from Amgen, BMS, Celgene, GSK, Johnson & Johnson, Pfizer, Sanofi, Takeda. LP declares no conflict of interest; VL had consultancy and received honoraria from Sanofi; TJ had consultancy and recieved honoraria or research funding from Amgen, Johnson & Johnson, Sanofi, Pfizer, BMS, GSK. JS had consultancy and received honoraria from Amgen, BMS, Celgene, GSK, Johnson & Johnson, Sanofi; AJ declares no conflict of interest; JR had consultancy and received honoraria from Amgen, BMS, GSK, Johnson & Johnson, Pfizer and Sanofi; PP had consultancy and received honoraria from Amgen, BMS, Celgene, GSK, Johnson & Johnson, Pfizer, Sanofi, Takeda, MS had consultancy and received honoraria from Johnson & Johnson, Pfizer, Sanofi; TP declares no conflict of interest; PK had consultancy and received honoraria from Amgen and Sanofi; TP received honoraria from Johnson&Johnson and Takeda. FS declares no conflict of interest; IS had consultancy/advisory role and received honoraria from Amgen, BMS, GSK, Pfizer, Johnson & Johnson, Sanofi,PJ had consultancy and received honoraria from AstraZeneca, BMS, GSK, Johnson & Johnson, Pfizer, AbbVie, Takeda, Novartis.; VC declares no conflict of interest; VM had consultancy/advisory role and received honoraria from Amgen, BMS, GSK, Pfizer, Johnson & Johnson, Sanofi, The Binding Site.; RH has had a consultant or advisory relationship with Janssen, Amgen, Celgene, AbbVie, BMS, Novartis, PharmaMar, and Takeda; has received honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda; has received research funding from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda.

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