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Dose/Schedule-Adjusted Rd-R vs Continuous Rd for elderly, intermediate-fit, newly diagnosed multiple myeloma patients

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Abstract:
Lenalidomide-dexamethasone (Rd) is a standard treatment for elderly multiple myeloma (MM) patients. In this randomized, phase III study, we investigated the efficacy and feasibility of a dose/schedule-adjusted Rd followed by maintenance 10 mg/day without dexamethasone (Rd-R) vs continuous Rd in elderly, intermediate-fit newly diagnosed MM patients.

The primary endpoint was event-free survival (EFS), defined as progression/death for any cause, lenalidomide discontinuation, any hematologic grade 4 or non-hematologic grade 3-4 adverse events (AEs).

Of the 199 evaluable patients, 101 received Rd-R and 98 continuous Rd. Median follow-up was 37 months. Best response rates were comparable: ≥ partial response rates were 78% vs 68% (p=0.15) in Rd-R vs continuous Rd groups. EFS was 10.4 with Rd-R vs 6.9 months with continuous Rd (HR 0.70, 95% CI 0.51-0.95, p=0.02). Median progression-free survival was 20.2 vs 18.3 months (HR 0.78, 95% CI 0.55-1.10, p=0.16), 3-year overall survival was 74% vs 63% (HR 0.62, 95% CI 0.37-1.03, p=0.06).

At least 1 non-hematologic grade ≥3 AE rate was 33% vs 43% (p=0.14); the most frequent grade ≥3 AEs were neutropenia (21% vs 18%), infections (10% vs 12%) skin disorders (7% vs 3%) in Rd-R vs Rd; constitutional and central nervous system AEs mainly related to dexamethasone were more frequent with continuous Rd. Lenalidomide was discontinued for AEs in 24% vs 30% and was reduced in 45% vs 62% of patients, in Rd-R vs Rd, respectively.

In intermediate-fit patients, switching to reduced-dose lenalidomide maintenance without dexamethasone after 9 cycles of Rd was feasible, with similar outcome to standard continuous Rd.

Conflict of interest: COI declared - see note

COI notes: A.L. has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and GSK; has served on the advisory boards for Bristol-Myers Squibb, Celgene, Janssen, and Takeda. G.G. has served on the advisory boards for Abbvie, Janssen and Astra-Zeneca, and Speaker's Bureau for Abbvie, Janssen. M.D.A. has served on the advisory board for GSK. M.O. has received honoraria from and served on the advisory boards for Amgen, BMS, Celgene, Janssen, Takeda. G.B. has received honoraria from Novartis, Celgene Amgen, Takeda. M.G. has received honoraria from Bristol-Myers-Squibb, Celgene, Janssen, Takeda. R.M. has received honoraria from Abbvie, Roche, Janssen, Shire. N.G. has received research grants from Celgene, Janssen Pharmaceutical; clinical trial sponsorship from Janssen Pharmaceutical, Millennium Pharmaceutical, GSK; served on the advisory boards for Celgene, Takeda, Janssen Pharmaceutical; and congress fee from Janssen Pharmaceutical, Celgene, Bristol-Myers Squibb. F.P. has served on the advisory boards for Celgene/ Bristol-Myers Squibb, Janssen. P.C. has served as speakers and/ or on the advisory

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Non-author contributions and disclosures: No;

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Dose/Schedule-Adjusted Rd-R vs Continuous Rd for elderly, intermediate-fit, newly diagnosed multiple myeloma patients.

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Running head: Rd-R vs continuous Rd in intermediate-fit NDMM

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Keypoint

Dose/schedule-adjusted Rd-R prolonged EFS, inducing similar PFS and OS compared with standard continuous Rd in intermediate-fit elderly NDMM

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Abstract

Lenalidomide-dexamethasone (Rd) is a standard treatment for elderly multiple myeloma (MM) patients. In this randomized, phase III study, we investigated the efficacy and feasibility of a dose/schedule-adjusted Rd followed by maintenance 10 mg/day without dexamethasone (Rd-R) vs continuous Rd in elderly, intermediate-fit newly diagnosed MM patients.

The primary endpoint was event-free survival (EFS), defined as progression/death for any cause, lenalidomide discontinuation, any hematologic grade 4 or non-hematologic grade 3-4 adverse events (AEs).

Of the 199 evaluable patients, 101 received Rd-R and 98 continuous Rd. Median follow-up was 37 months. Best response rates were comparable: ≥ partial response rates were 78% vs 68% (p=0.15) in Rd-R vs continuous Rd groups. EFS was 10.4 with Rd-R vs 6.9 months with continuous Rd (HR 0.70, 95% CI 0.51-0.95, p=0.02). Median progression-free survival was 20.2 vs 18.3 months (HR 0.78, 95% CI 0.55-1.10, p=0.16), 3-year overall survival was 74% vs 63% (HR 0.62, 95% CI 0.37-1.03, p=0.06).

At least 1 non-hematologic grade ≥3 AE rate was 33% vs 43% (p=0.14); the most frequent grade ≥3 AEs were neutropenia (21% vs 18%), infections (10% vs 12%) skin disorders (7% vs 3%) in Rd-R vs Rd; constitutional and central nervous system AEs mainly related to dexamethasone were more frequent with continuous Rd. Lenalidomide was discontinued for AEs in 24% vs 30% and was reduced in 45% vs 62% of patients, in Rd-R vs Rd, respectively.

In intermediate-fit patients, switching to reduced-dose lenalidomide maintenance without dexamethasone after 9 cycles of Rd was feasible, with similar outcome to standard continuous Rd.

Keywords: Multiple myeloma, intermediate-fit, elderly, lenalidomide, dexamethasone

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Introduction

The International Myeloma Working Group (IMWG) frailty score identifies fit, intermediate-fit and frail multiple myeloma (MM) patients with different survival and risk of toxicity from treatments in newly diagnosed MM (NDMM). According to the score, intermediate-fit patients are aged 76 to 80 years or younger patients with an impairment in functional abilities (Activities of Daily Living [ADL] ≤ 4 or Instrumental Activities of Daily Living [IADL] ≤ 5) or comorbidities (Charlson Comorbidity Index [CCI] ≥ 2).[1]

Combination therapies including lenalidomide-dexamethasone (Rd), bortezomib-melphalan-prednisone (VMP) and bortezomib-lenalidomide-dexamethasone (VRd)[2–4] are considered standard treatment options for elderly patients not eligible for autologous stem-cell transplantation (ASCT).[2–4] Monoclonal antibody-based treatments including daratumumab plus either Rd or VMP[5,6] have been approved by EMA and FDA and have recently become new standards of care in this setting.

Rd is effective and safe in elderly NDMM patients of all ages. However, the outcome of patients older

than 75 years in the FIRST trial was suboptimal as compared to younger patients (progression-free survival [PFS] 20 vs 28 months, overall survival [OS] 52 vs 60.9 months).[2,7] The impact of age on efficacy was less evident in the MAIA trial, in which the outcome of Rd in <75 and ≥75 years patients was comparable (median PFS: 32 vs 34 months).[8]

Although life expectancy should be considered, there is a large variability within the same age group (i.e. from 4.9 to 14.2 years in the 75 years-old population), reflecting health status variability.[9]

Clinical trials usually have stringent eligibility criteria and myeloma patients 75 years or older, or with comorbidities and functional impairments are an understudied population. In the FIRST and MAIA trials,[2,6] which led to the approval of Rd and daratumumab-Rd, median age was 73 years, with 35% and 43.5% of patients older than 75 years, respectively. Nevertheless, patients with ECOG performance status >2 or with impaired organ function (e.g. significant cytopenia or hepatic impairment) were excluded. Furthermore, older patients are more susceptible to adverse events (AEs) that may negatively affect the duration of treatment and outcome, due to increased comorbidities, altered pharmacodynamics and functional impairments.[10] Standard treatments may induce a high rate of grade 3-4 AEs (75-91%), thus determining a discontinuation due to AEs in 30% of patients.[2,3,11–13]

Continuous therapy such as Rd or daratumumab-Rd until progressive disease (PD) and daratumumab-VMP followed by daratumumab maintenance until PD proved to be more effective compared to fixed duration therapy.[5,7] Currently, there are no clear data on the advantage of continuous steroid treatment compared with fixed-duration treatment in NDMM. Nevertheless, steroids are scarcely tolerated in the long term, even in younger patients,[14] and whether sparing dexamethasone is as effective as a prolonged steroid-exposure remains an open issue.

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In the FIRST trial, among patients older than 75 years treated with continuous Rd, one third discontinued lenalidomide and 44% needed a dose reduction. Moreover, at 18 months, only 30% of patients ≥ 75 years old were receiving full planned dose of lenalidomide.[7] In the EMN01 study, in which lenalidomide dose was reduced to 10 mg during maintenance after a full-dose induction, median PFS in intermediate-fit patients was 16.6 months, 16% of patients discontinued treatment due to AEs and 16% reduced lenalidomide.[15,16] Thus, reducing the dose of lenalidomide after induction seems a valuable strategy to improve the feasibility of treatment in elderly intermediate-fit patients.

Therefore, we designed a trial for elderly intermediate-fit NDMM patients and compared Rd induction followed by R maintenance 10 mg/day without steroids (Rd-R) vs standard continuous Rd. We aimed to evaluate if Rd schedule can be further optimized and if avoiding continuous steroids is a more appropriate strategy in this group of patients.

Methods

Study patients

Patients with NDMM aged > 65 and ≤ 80 years old, ineligible for autologous stem cell transplantation (ASCT) and defined intermediate-fit according to the IMWG frailty score (score=1) could be enrolled.[1] Fit (IMWG frailty score=0) and frail (score≥2) patients were excluded from the trial. The definition of intermediate-fit patients based on age, CCI, ADL and IADL scores is summarized in Table 1.

Inclusion criteria were measurable and symptomatic disease. Patients could be enrolled regardless of abnormal baseline laboratory values (e.g. absolute neutrophil count <1*10^9/L, platelet count <80*10^9/L, haemoglobin <8 g/dL, creatinine clearance <30 mL/min), in order to include those who are generally excluded from clinical trials. Exclusion criteria were the presence of another malignancy, uncontrolled active infection and active hepatitis B or C and HIV infection. Patients agreed to use contraception throughout the study. The study was approved by the institutional review board at each of the participating centres. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki and is registered on ClinicalTrials.gov as NCT02215980.

Study design and intervention

This is a multicentre randomized (1:1) phase III clinical trial that involved 33 Italian centres. The primary endpoint was event-free survival (EFS); secondary endpoints included progression-free survival (PFS), overall survival (OS), response rate, and incidence of dose reductions and drug discontinuation.

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Patients randomized to Rd-R received nine 28-day induction cycles of lenalidomide (25 mg per day for 21 days) and dexamethasone (20 mg on days 1, 8, 15, and 22) followed by lenalidomide maintenance (10 mg per day for 21 days) until progression or intolerance. Patients allocated to continuous Rd received 28-day cycles of lenalidomide (25 mg per day for 21 days) and dexamethasone (20 mg on days 1, 8, 15, and 22) until progression or intolerance, as adopted in patients >75 years in the FIRST trial.[7] Anti-thrombotic prophylaxis was mandatory during lenalidomide therapy: aspirin or low molecular weight heparin were chosen according to the thrombotic risk of the patient.[17] Granulocyte colony-stimulating factor (GCSF), blood and platelet transfusions were allowed during the study. In case of neutropenia or recurrent infections, antibacterial prophylaxis was recommended but not mandatory. Treatment was discontinued in case of withdrawal of consent, disease progression, or adverse events that in the Investigator opinion could cause severe or permanent harm to the patient. Less serious toxicities were managed through dose reductions of the study drugs.

Assessments of endpoint

The primary endpoint of the study was EFS, which was defined as the occurrence of grade 4 hematologic AEs, grade 3-4 non hematologic AEs including second primary malignancy (SPM), discontinuation of lenalidomide, disease progression or death. EFS was calculated from the time of enrolment until the occurrence of any of the defining events mentioned above, whichever came first. PFS was calculated from the time of enrolment until the date of disease progression or death for any cause, whichever came first. OS was calculated from the time of enrolment until the date of death for any cause. Patients who did not experience any event were censored at the date of last follow-up. Evaluation of response to the treatment was performed according to the International Response Criteria for Multiple Myeloma.[18] AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Efficacy assessment was performed every 4 weeks during study treatment. Safety assessment was performed every 2 weeks for the first 9 cycles and every 4 weeks thereafter. The lead/corresponding author analyzed the data and all authors had access to primary clinical trial data and approved the manuscript.

Statistical analysis

The study was designed to compare EFS between patients in the experimental Rd-R arm vs standard continuous Rd arm. With a one-sided alpha error of 0.05, a sample size of 210 patients was determined to provide a power of 80% to detect a hazard ratio (HR) of 0.62 in favour of Rd-R, assuming 2 years of accrual, study duration of 5 years, and 15% drop-outs. Two-hundred-ten patients were needed to yield the necessary number of events (n=139) for the primary analysis,

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calculated with the Schoenfeld formula. Patients were analyzed on an intention-to-treat (ITT) basis for all time to event endpoints. Interim safety analyses were planned when the first 50 patients completed the first cycle and the first year of treatment. Response rates and safety were analyzed in patients receiving at least one dose of study drugs. Kaplan-Meier curves were generated for all time-to-event endpoints and long-rank test was used to compare treatment arms. The Cox proportional hazard model, adjusted for the main prognostic factor (chromosomal abnormalities, lactate dehydrogenase [LDH], International Staging System [ISS]) and age (>75 vs ≤75 years), was used to estimate HR values and the 95% confidence intervals (CI) for the ITT population. Response rates and AEs rates were compared using the Fisher's test. Times of observation were censored on March 4, 2020. Data were analysed using R software (version 3.6.2).

Data Sharing Statement

Requests of data and analyses performed in this study should be addressed directly to the corresponding author, who will evaluate the request and can provide the requested information.

Results

A total of 210 patients were enrolled between October 28, 2014 and October 3, 2017. Eleven patients did not meet the inclusion criteria and were excluded from the analysis. One-hundred-ninety-nine patients were randomized to Rd-R (n=101) or continuous Rd (n=98) and could be evaluated (Figure 1).

Patient and disease characteristics were well balanced between the 2 arms (Table 2). Median age was 75 years in the Rd-R arm and 76 years in the Rd arm (p=0.06); 21% and 26% of patients were ISS-3 stage (p=0.5) and 19% vs 23% had high-risk chromosomal abnormalities (p=0.68); 52% of patients in the Rd-R and 43% in the Rd groups were defined intermediate-fit not for age but for geriatric impairments (CCI or ADL or IADL) only.

Efficacy

After a median follow-up of 37 months (range 27-45 months), the median EFS was 10.4 months in the Rd-R arm and 6.9 months in the Rd arm (HR 0.70, 95% CI 0.51-0.95, p=0.02) (Figure 2A). The EFS advantage in Rd-R arm was maintained beyond cycle 9 (median: 19.8 vs 10.6 in Rd-R vs Rd, HR 0.55, 95% CI 0.32-0.93, p=0.03) (Figure 3).

Overall, grade 4 hematologic AEs occurred in 8%, grade 3-4 non hematologic AEs including SPM in 37%, discontinuation of lenalidomide in 14%, and PD or death in 42% of patients. G4 hematologic toxicities were 11% vs 6%, G3-4 non-hematologic AEs were 31% versus 40%, discontinuation of lenalidomide was 16% versus 11% in Rd-R versus continuous Rd. No difference

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in terms of EFS was observed in patients considered intermediate-fit according to age vs intermediate-fit for comorbidities or functional impairments (median EFS: 8.1 vs 7.6 months, HR 0.93, 95% CI 0.68-1.28, p=0.67).

The median PFS was 20.2 months with Rd-R and 18.3 months with Rd (HR 0.78, 95% CI 0.55-1.1, p=0.16) (Figure 2B). A total of 70 patients died (32 in the Rd-R and 38 in the Rd arms), mainly due to PD (15 patients in each group) The median OS was not reached; the 3-year OS was 74% with Rd-R and 63% with continuous Rd (HR, 0.62; 95%CI, 0.37-1.03; p=0.06) (Figure 2C).

Among patients still on therapy after 9 cycles, no difference in median PFS was observed between Rd-R and Rd (24.3 vs 18.7 months, HR 0.73; 95% CI 0.44-1.18; p=0.19).

Best response was similar in the 2 groups, the overall response rate (at least partial response during the whole treatment period) was 78% vs 68% (p=0.15), ≥ very good partial response rate was 51% vs 39% (p 0.09) in Rd-R vs continuous Rd arm. (Table 3). Median time to response was 2 vs 1.9 months and median time to best response was 7.5 vs 6.8 months in Rd-R and Rd arms, respectively. Among patients still on therapy after 9 cycles, 17% in Rd-R and 25% in Rd arm (p=0.2) improved their response thereafter.

A trend towards a PFS benefit in favour of Rd-R was observed in standard-risk patients (HR 0.62; 95% CI 0.39-1.00), but not in high-risk patients (HR 1.10; 95% CI 0.47-2.55).

Safety

Median duration of lenalidomide treatment was 17.3 months with Rd-R (IQR 7.2-34.7) and 12.8 months with continuous Rd (IQR 4.5-30.3). Median duration of dexamethasone treatment was 8.6 (IQR 7.5-9.3) vs 11.7 (IQR 4.9-25.3) months, respectively. Median cumulative dose delivered of lenalidomide was 5798 mg in Rd-R and 5408 mg in Rd arms. As expected, due to the study design, median cumulative dose delivered of dexamethasone was inferior in Rd-R as compared to Rd arm (720 mg vs 955 mg).

At least 1 grade ≥3 hematologic AE was reported in 26% of Rd-R and 20% of Rd patients (p=0.40). The most frequent grade ≥3 hematologic toxicity was neutropenia: 21% vs 18%, respectively.

The most frequent grade ≥3 toxicities were non-hematologic. At least 1 grade ≥3 non-hematologic AE was reported in 33% of Rd-R and 43% of Rd patients (p=0.15). The most frequent grade ≥3 non-hematologic toxicities in Rd-R vs Rd arm were infections (10% vs 12%), constitutional (3% vs 12%), dermatologic (7% vs 3%), and central nervous toxicities (2% vs 6%), and no significant differences were detected among the two arms. Granulocyte colony-stimulating factor was administered in 20% of Rd-R and 17% of Rd patients (p=0.72). A low incidence of grade ≥3 thromboembolic events (1% in Rd-R, and 4% in Rd patients) was recorded. Overall, 63 patients (32%) received low-molecular-weight heparin, 65 (33%) aspirin, 18 (9%) warfarin, 7 (3%) did not receive any prophylaxis, and the prophylaxis is unknown in the remaining 46 (23%) patients. Grade ≥3 peripheral neuropathy was not significant in any of the arms. Four SPMs were recorded, 2 (2%) with Rd-R and 2 (2%) with Rd (1 pancreatic neoplasm, 1 Bowen disease, 1 prostatic cancer and 1

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Hodgkin lymphoma). One patient in the Rd-R group was diagnosed with a gastric cancer few days after starting cycle 1 (Table 4). Among patients still on therapy after cycle 9, the rate of at least 1 grade ≥3 non hematologic AEs was 17% vs 25% (p= 0.28), the most frequent AEs were constitutional (fatigue 1% vs 3%) and gastrointestinal (diarrhea 3% vs 7%) in Rd-R vs continuous Rd, respectively.

After 9 cycles, the cumulative incidence of grade ≥3 hematological AEs at 2 years was 16% vs 13% in Rd-R arm vs Rd; the cumulative incidence of non-hematological toxicity at 2 years was inferior in Rd-R arm vs Rd (10% vs 17%) (Supplementary Figure 1A-1B).

The rate of lenalidomide discontinuation for AE was 24% with Rd-R vs 30% with continuous Rd (p=0.42). Lenalidomide was reduced in 45 (45%) and 61 (62%) patients (p=0.01), and dexamethasone in 17 (17%) and 30 (31%) patients, respectively (Table 4). In detail, 40 and 48 patients had at least one lenalidomide dose reduction in the first 9 cycles in Rd-R vs Rd (including patients starting lenalidomide at reduced dose). Fifteen and 20 patients had at least one lenalidomide dose reduction beyond cycle 9 in Rd-R vs Rd. Regarding dexamethasone, 17 and 22 patients had at least one dose reduction in the first 9 cycles in Rd-R vs Rd, whereas 8 patients reduced dexamethasone beyond cycle 9 in the continuous Rd group. During the first 60 days from the start of therapy, early drop-out occurred in 9% of patients; causes included: toxicity (50%) and toxic deaths (16%), decline of patient conditions or lost to follow-up (17%), death not related to PD (11%) and PD (6%). The main causes of early discontinuation due to toxicities were infections (38%).

Overall, 40 deaths not related to PD occurred: 17 in the Rd-R (17%) and 23 in the Rd (23%). Of these, 13 occurred while on treatment and were considered related to study drugs (5 in Rd-R: 2 pneumonia, 1 COPD exacerbation, 1 Escherichia Coli infection and 1 sepsis; 8 in continuous Rd: 3 sepsis, 1 E. Coli infection, 1 post-surgical infection, 1 respiratory failure, 1 cardiac arrest and 1 heart failure), 5 due to decline of medical conditions (2 in Rd-R and 3 in Rd), 3 accidental deaths, 13 unknown and 6 for other diseases.

At the time of analysis, 58 (29%) patients were still on therapy, 34 (34%) in Rd-R and 24 (24%) in Rd. Overall, 141 (71%) patients had discontinued treatment, 67 (66%) in Rd-R and 74 (75%) in Rd arm. Main reasons for discontinuation were PD (51% vs 46% in Rd-R vs Rd) and toxicity (13% vs 28% in Rd-R vs Rd); overall 61% of patients received a second-line therapy, mainly bortezomib-based (81%).

Discussion

This is the first randomized phase III trial that compared an adapted Rd-R treatment schedule sparing steroids and reducing lenalidomide-dose at maintenance, with the standard continuous Rd, in intermediate-fit NDMM patients ineligible for ASCT. After a median follow-up of 37 months, no difference in PFS and OS was noticed between Rd-R and continuous Rd, whereas EFS

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(accounting for a combination of toxicity and efficacy) was significantly prolonged in the Rd-R arm. Furthermore Rd-R resulted in better tolerability compared to Rd, particularly in terms of non-hematologic toxicity (Grade ≥3: 33% vs 43%), and lenalidomide dose reductions (45% vs 62%).

The combination of lenalidomide and dexamethasone is an effective treatment in transplant-ineligible NDMM patients.[2] Toxicity is one of the major concerns in intermediate-fit and frail patients, since they are at higher risk of AEs, leading to treatment discontinuations.[1] The goal of treatment for intermediate-fit patients is to achieve deep responses and reduce toxicity, while preserving quality of life.[19] How to appropriately modulate treatment intensity in this group of patients has been investigated in small trials, but a definitive strategy has not yet been determined.[20–22] Therefore, in order to account for both efficacy and safety, we chose EFS as primary endpoint of our study. In our trial, EFS curves already dissociate within the first 9 months, when the treatment doses and schedule were similar between the two arms. Despite the same initial treatment, the median age of patients at baseline was 75 and 76 years, and 21% and 25% of patients were ISS-3 stage, in the Rd-R and Rd arms, respectively. Although these differences were minor and not significant, they might in part explain the EFS difference during the first 9 months in this particular population. Nevertheless, beyond cycle 9, the EFS advantage favoring Rd-R arm remained significant, supporting the feasibility of reducing treatment intensity over time. The early interruption of dexamethasone in Rd-R arm and lenalidomide dose reduction to 10 mg as maintenance following the first 9 cycles, did not affect the efficacy of this regimen.

In the FIRST trial, patients >75 years old receiving continuous Rd were 35% and in the EMN01 trial patients >75 years treated with Rd for 9 cycles followed by lenalidomide maintenance were 37%; furthermore, 26% of patients in the EMN01 trial were intermediate-fit. In our trial, 52% of patients were >75 years and all the patients were intermediate-fit.[7,15,16] As reported in the sub-analysis of the FIRST trial including patients >75 years, median PFS was 20 months with continuous Rd, and in intermediate-fit patients enrolled in the EMN01 trial PFS was 16.6 months. Despite the limitations of cross-trial comparisons, our results are comparable to those reported in the FIRST and EMN01 trials: our gentler approach with a dose/schedule-adjusted Rd-R induced a median PFS of 20.2 months.

Despite no substantial PFS difference between Rd-R vs continuous Rd, a trend towards a better PFS was observed in standard-risk patients treated with Rd-R vs Rd, whereas no difference was observed in high-risk patients, although limited by a lower number of patients. There is no evidence that lenalidomide improves the outcome of patients with high-risk cytogenetics;[2,23] triplets or more intensive regimens including newer drugs[5,6,24] are needed to overcome their bad prognosis. However, the feasibility and tolerance of more intensive regimens should be carefully considered in high-risk intermediate-fit patients, and more data are needed. In standard-risk patients, a reduced dose Rd-R can be the appropriate strategy to balance efficacy and safety.

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In our study, the safety profile of lenalidomide-dexamethasone was consistent to those observed in previous studies.[7,16] A low incidence of venous thromboembolism and SPM was observed. The major hematologic toxicity was neutropenia, which was slightly higher with Rd-R probably due to the absence of steroids during maintenance. However, this did not translate in a higher rate of infections.

The main grade ≥3 non-hematologic toxicity in both arms was infection, with a rate similar to that reported in the EMN01 trial (9%) and inferior to that reported in the sub-analysis of the FIRST trial (29%). Central nervous system AEs and general symptoms were slightly higher with continuous Rd, likely due to the longer administration of dexamethasone. In the Rd arm, 31% of patients needed to reduce dexamethasone for AEs (as compared to 17% in Rd-R), confirming that steroids are scarcely tolerated, particularly in these elderly patients, and they might hamper treatment adherence.[14]

Early drop-out rate (e.g. within the first 60 days) in our study was 9%, primarily due to early toxicities, mostly infections. Overall, 6.5% of patients died due to toxicity, and infections were the most frequent cause of toxic deaths (10 patients died for infections among 13 toxic deaths). In a large population of NDMM patients, the incidence of toxic deaths was 5% in patients aged 75–79 years.[25]

Indeed, infections are an important cause of morbidity and mortality in MM patients. In our study, antimicrobial prophylaxis was recommended in case of neutropenia or recurrent infections but not mandatory. As reported in a recent phase 3 trial, the addition of prophylactic levofloxacin to active myeloma treatment during the first 12 weeks of therapy significantly reduced febrile episodes and deaths compared with placebo, particularly in transplant-ineligible patients (HR 0.51).[26] In the future, an adequate antibiotic prophylaxis at least for the first 12 weeks of therapy is warranted, especially for intermediate-fit and frail patients.

Our analysis has some limitations. The trial was designed with EFS as primary endpoint and thus has not enough power to detect a statistically significant difference in PFS. However, the outcome of the 2 arms is comparable. No stratification at randomization was planned according to prognostic factors and intermediate-for age or for geriatric impairments. However, patient characteristics were well balanced between the 2 groups. Rd is quite an old treatment and newer combinations are being explored for intermediate-fit NDMM;[22] still, our results provide practical insight in the management of these patients and confirm that sparing steroids after 9-12 months, often adopted in clinical practice, is a feasible strategy. This strategy could be further evaluated in the future as a starting point for newer combinations including novel agents (a trial comparing daratumumab-lenalidomide vs Rd in frail patients is underway - NCT03993912).

In conclusion, we confirmed the efficacy and feasibility of continuous lenalidomide therapy. An optimization of this combination, sparing steroids and reducing lenalidomide dose after induction (Rd-R) can allow patients to remain on treatment longer, maintaining disease control over time.

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Our results suggest that, at least in intermediate-fit elderly NDMM patients, treatment intensity during continuous treatment can be de-escalated without a negative impact on outcome. Ongoing and future trials including “frailty-adjusted” strategies to optimize treatment in the era of personalized therapy will evaluate this steroid-free approach also with newer drugs and combinations.

Author contribution: A.L., M.B., S.B. conceived, planned and supervised the study; A.L. collected and analyzed the data; A.C. performed the statistical analysis; all authors provided patients and/or study materials; A.L. wrote the manuscript and all authors provided comments and final approval.

Disclosure of conflicts of interest

A.L. has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and GSK; has served on the advisory boards for Bristol-Myers Squibb, Celgene, Janssen, and Takeda. G.G. has served on the advisory boards for Abbvie, Janssen and Astra-Zeneca, and Speaker’s Bureau for Abbvie, Janssen. M.D.A. has served on the advisory board for GSK. M.O. has received honoraria from and served on the advisory boards for Amgen, BMS, Celgene, Janssen, Takeda. G.B. has received honoraria from Novartis, Celgene Amgen, Takeda. M.G. has received honoraria from Bristol-Myers-Squibb, Celgene, Janssen, Takeda. R.M. has received honoraria from Abbvie, Roche, Janssen, Shire. N.G. has received research grants from Celgene, Janssen Pharmaceutical; clinical trial sponsorship from Janssen Pharmaceutical, Millennium Pharmaceutical, GSK; served on the advisory boards for Celgene, Takeda, Janssen Pharmaceutical; and congress fee from Janssen Pharmaceutical, Celgene, Bristol-Myers Squibb. F.P. has served on the advisory boards for Celgene/ Bristol-Myers Squibb, Janssen. P.C. has served as speakers and/ or on the advisory boards for AbbVie, ADC Theraputics, Amgen, Celgene, Daiichi Sankyo, Gilead, Incyte, Janssen, Jazz Pharmaceutics, Kite, KiowaKirin, Novartis, Roche, Sanofi, Servier, Takeda. P.T. has received honoraria from Janssen, Celgene, Bristol Myers Squibb, Amgen, Takeda, AbbVie and Oncopeptides. MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and AbbVie; has served on the advisory boards for Janssen and GSK; has received research funding from Sanofi, Celgene, Amgen, Janssen, Novartis, Bristol-Myers Squibb, and Mundipharma. SB has received honoraria from Celgene, Amgen and Janssen, and Bristol-Myers Squibb; has served on the advisory boards for Celgene, Amgen, Janssen, and Karyopharm; has received consultancy fees from Janssen and Takeda.

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Table 1. IMWG frailty score to define patient's frailty status.

Parameter	Score
Age	
≤75 years	**0**
76-80 years	**1**
> 80 years	**2**
ADL	
> 4	**0**
≤4	**1**
IADL	
> 5	**0**
≤ 5	**1**
CCI	
≤ 1	**0**
≥ 2	**1**
Patients status	
FIT	**0**
INTERMEDIATE FITNESS	**1**
FRAIL	**≥ 2**

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; CCI, Charlson Comorbidity Index.

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Table 2. Baseline patient and disease characteristics

	Rd-R (n=101)	Rd (n=98)	All patients (n=199)
AGE, median (IQR)	75 (73-77)	76 (74-79)	76 (73-78)
76-80 years old n (%)	48 (48)	56 (57)	104 (52)
SEX			
Male n (%)	53 (52)	49 (50)	102 (51)
Female n (%)	48 (48)	49 (50)	97 (49)
ECOG PS n (%)			
0	35 (37)	36 (37)	71 (37)
1	50 (52)	51 (53)	101 (52)
2	11 (11)	10 (10)	21 (11)
Missing	5	1	6
Creatinine clearance n (%)			
≤ 60 mL/min	36 (36)	48 (49)	84 (42)
> 60 mL/min	65 (64)	50 (51)	115 (58)
ISS n (%)			
I	32 (32)	37 (38)	69 (35)
II	48 (47)	36 (37)	84 (42)
III	21 (21)	25 (25)	46 (23)
Chromosomal abnormalities n (%)			
Standard risk	55 (81)	56 (77)	111 (79)
High risk*	13 (19)	17 (23)	30 (21)
Data Missing**	33	25	58
Amp1q	25 (38)	34 (49)	59 (44)
Intermediate-Fit n (%)			
for age	48 (48)	56 (57)	104 (52)
for geriatric impairment			
CCI ≥2	23 (23)	17 (18)	40 (20)
ADL ≤ 4	9 (9)	12 (12)	21 (11)
IADL ≤ 5	21 (21)	13 (13)	34 (17)

Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; Rd, continuous lenalidomide-dexamethasone; ECOG PS, European Eastern Cooperative Group Performance Status; ISS, international staging system; FISH, fluorescent in situ hybridization; CCI, Charlson Comorbidity Index; ADL, activity of daily living; IADL, instrumental ADL. % calculated on the N of patients whose data were available.

* At least one among del17, or t(14;16) or t(4;14).

** data about del17, or t(14;16) or t(4;14) missing.

*** positivity cut-off for del17 10%, for t(14;16) or t(4;14) 15%.

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Table 3. Best response rates

BEST RESPONSE	Rd-R (n=101) n (%)	Rd (n=98) n (%)	All (n=199) n (%)
ORR	79 (78)	67 (68)	146 (73)
≥ VGPR	52 (51)	38 (39)	90 (45)
sCR	4 (4)	-	4 (2)
CR	1 (1)	1 (1)	2 (1)
nCR*	19 (19)	15 (15)	34 (17)
VGPR	28 (28)	22 (22)	50 (25)
PR	27 (27)	29 (30)	56 (28)
SD	12 (12)	17 (17)	29 (15)
PD	-	6 (6)	6 (3)
Not evaluable	10 (10)	8 (8)	18 (9)

ORR, overall response rate; VGPR, very good partial response; sCR, stringent complete response; CR, complete response; nCR, near complete response; PR, partial response; SD, stable disease; PD, progressive disease; Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; Rd, continuous lenalidomide-dexamethasone; * immunofixation negative, bone marrow examination not performed.

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Table 4. Grade ≥3 AEs, drug discontinuation, dose reduction and cumulative dose.

	Rd-R (n=101) n (%)	Rd (n=98) n (%)	All (n=199) n (%)
Hematologic			
At least one event	26 (26)	20 (20)	46 (23)
Anemia	9 (9)	3 (3)	12 (6)
Neutropenia	21 (21)	18 (18)	39 (20)
Thrombocytopenia	4 (4)	2 (2)	6 (3)
Non hematologic			
At least one event	33 (33)	42 (43)	75 (38)
Cardiologic	2 (2)	2 (2)	4 (2)
Atrial fibrillation	1 (1)	1 (1)	2 (1)
Heart failure	1 (1)	1 (1)	2 (1)
Infection	10 (10)	12 (12)	22 (11)
Pneumonia	7 (7)	4 (4)	11 (6)
Febrile neutropenia	3 (3)	1 (1)	4 (2)
Sepsis/septic shock	0	5 (5)	5 (3)
Other	1 (1)	3 (3)	4 (2)
Constitutional	3 (3)	12 (12)	15 (8)
Fatigue	2 (2)	7 (7)	9 (5)
Fever	0	1 (1)	1 (1)
Other	1 (1)	6 (6)	7 (4)
Dermatologic	7 (7)	3 (3)	10 (5)
Rash	5 (5)	2 (2)	7 (4)
Other	2 (2)	1 (1)	3 (2)
Gastrointestinal	5 (5)	5 (5)	10 (5)
Diarrhea	3 (3)	4 (4)	7 (4)
Other	3 (3)	2 (2)	5 (3)
Nervous	2 (2)	6 (6)	8 (4)
Anxiety	0	2 (2)	2 (1)
Confusion	0	1 (1)	1 (1)
Insomnia	0	1 (1)	1 (1)
Tremor	0	2 (2)	2 (1)
Stroke	1 (1)	0	1 (1)
Other	1 (1)	4 (4)	5 (3)
Vascular	2 (2)	4 (4)	6 (3)
Thromboembolism	1 (1)	4 (4)	5 (3)
Other	1 (1)	1 (1)	2 (1)
SPM	2 (2)	2 (2)	4 (2)
Pancreatic	1 (1)	0	1 (1)
Hodgkin Lymphoma	0	1 (1)	1 (1)
Bowen Disease	1 (1)	0	1 (1)
Prostate	0	1 (1)	1 (1)
At least one lenalidomide dose reduction§	45%	62%	53%
Lenalidomide discontinuation for AEs	24%	30%	27%
Lenalidomide cumulative dose	5798 mg	5408 mg	5524 mg
Dexamethasone dose reduction*	17%	31%	24%
Dexamethasone discontinuation for AEs*	14%	34%	24%
Dexamethasone cumulative dose*	720 mg	955 mg	740 mg

§ Including patients who started lenalidomide at reduced dose. *As planned in the study design, dexamethasone was stopped in Rd-R arm after 9 cyles. Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; Rd, continuous lenalidomide-dexamethasone; SPM, second primary malignancy; AEs, adverse events. All AEs in the table were considered treatment-related or unknown according to the treating physicians.

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Figure Legend

Figure 1. Patient disposition.

Rd-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; Rd, continuous lenalidomide-dexamethasone

Figure 2. A) Event-free survival; B) Progression-free survival; C) Overall survival.

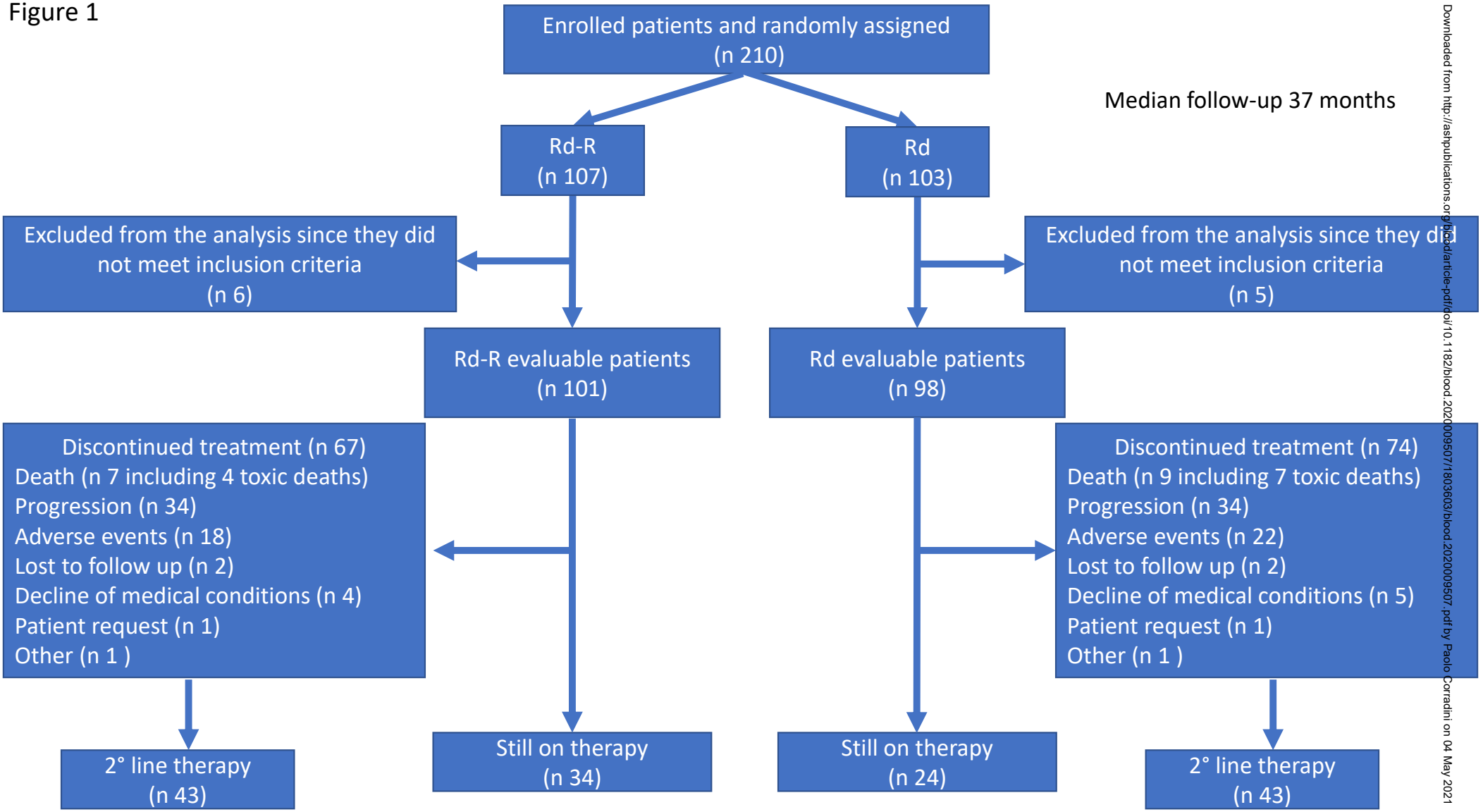
RD-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; RD, continuous lenalidomide-dexamethasone

Figure 3. Event-free survival from start of maintenance (cycle 10).

RD-R, lenalidomide-dexamethasone followed by lenalidomide maintenance; RD, continuous lenalidomide-dexamethasone

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Figure 1



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Figure 2A

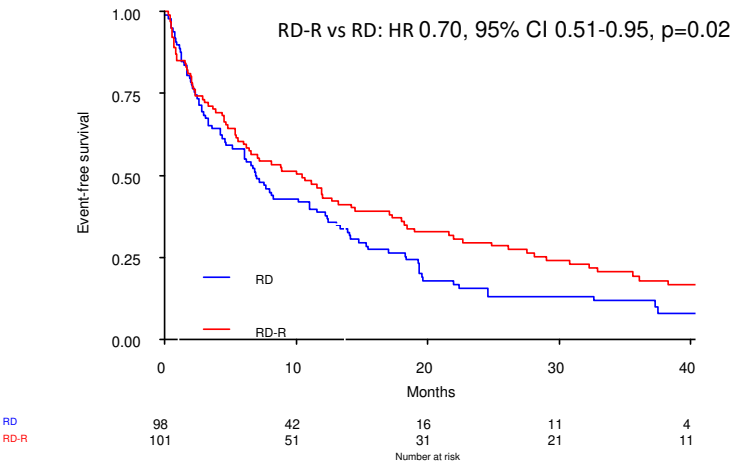


Figure 2B

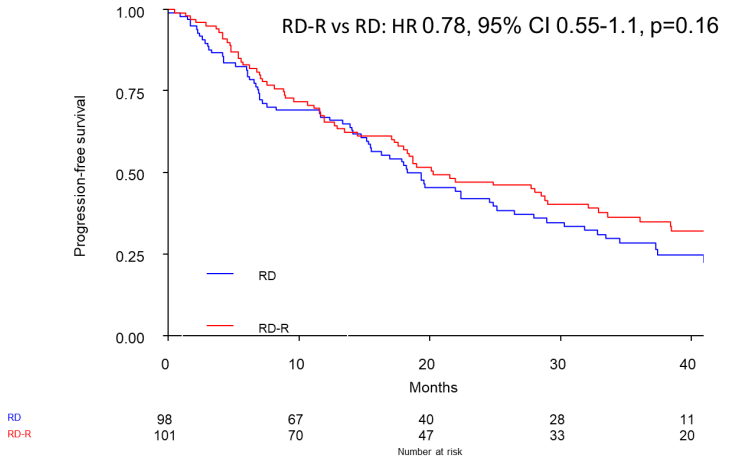
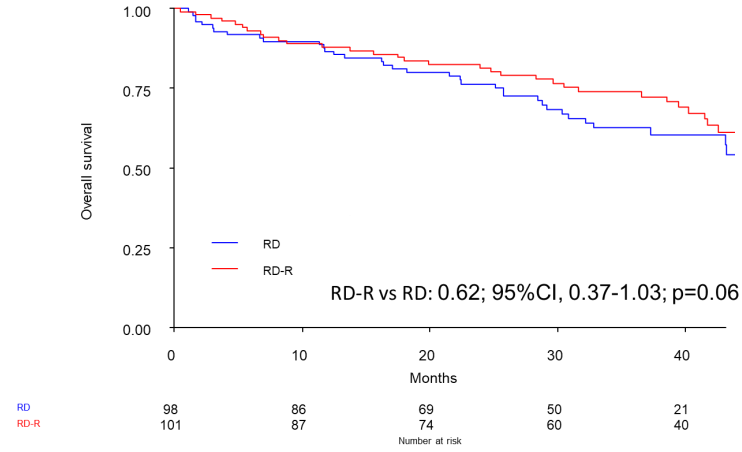
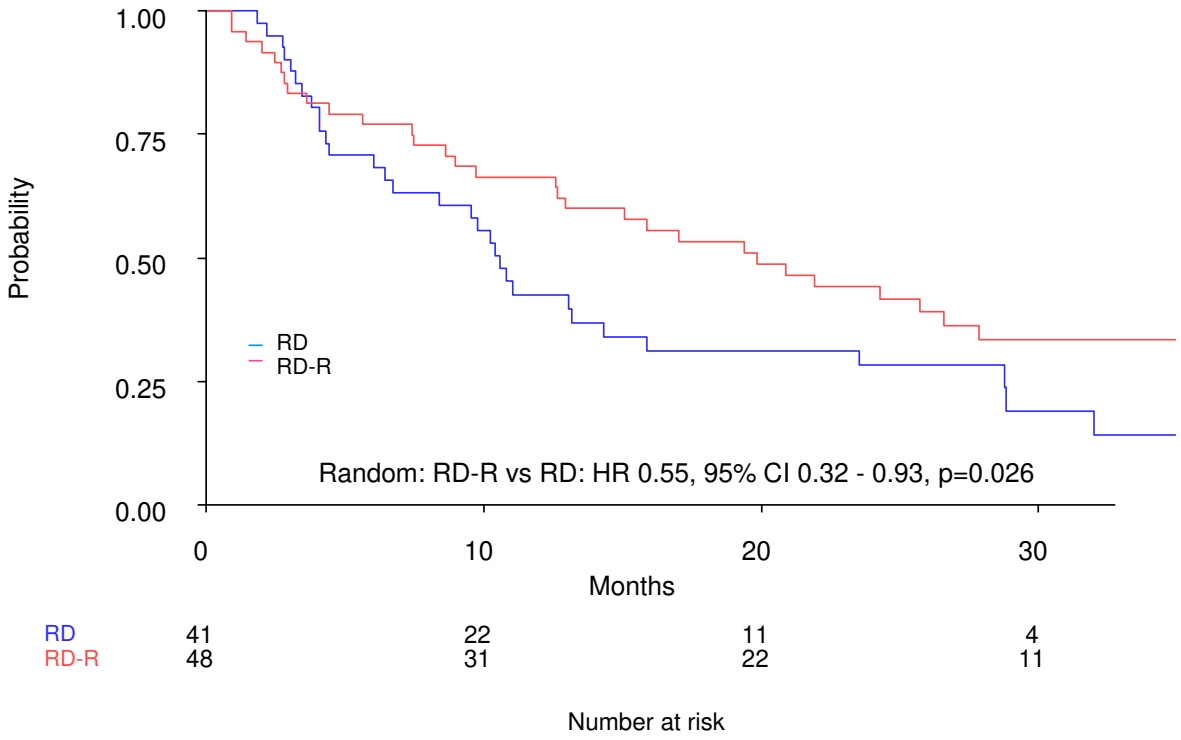


Figure 2C



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Figure 3



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