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Lenalidomide-based triplet regimens in first relapsed multiple myeloma patients: real-world evidence from a propensity score matched analysis

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Abstract
Lenalidomide and dexamethasone (Rd)-based triplets, in particular Carfilzomib-Rd (KRd) and Daratumumab-Rd (DaraRd), represent a standard of care in lenalidomide sensitive multiple myeloma (MM) patients in first relapse. Meta-analysis of randomized clinical trials (RCT), suggested better outcome with DaraRd. Trying to address this issue in clinical practice, we collected data of 430 consecutive MM patients addressed to Rd-based triplets in first relapse between January 2017 and March 2021. Overall, the most common used regimen was DaraRd, chosen in almost half of the cases (54.4%), followed by KRd (34.6%). Different triplets were used much less commonly. In the attempt to limit the imbalance of a retrospective analysis, we conducted a propensity score matching (PSM) comparison between DaraRd and KRd. After PSM, efficacy of DaraRd vs KRd was similar in terms of overall response rate (ORR) (OR: 0.9, p=0.685) as well as of very good partial response (VGPR) or better (OR: 0.9, p=0.582). The median progression-free survival (PFS) was significantly longer for DaraRd (29.8 vs 22.5 months; p=0.028). DaraRd was better tolerated, registering a lower rate of grade 3-4 non-hematological toxicity (OR: 0.4, p<0.001). With the limitations of any retrospective analysis, our real-life PSM comparison between DaraRd and KRd, in first relapse MM patients, showed better tolerability and prolonged PFS of DaraRd, although with some gap of performance, in particular of DaraRd, with respect to RCT. Carfilzomib containing regimens, like KRd, still remain a valid second-line option in the emergent scenario of first line Daratumumab-based therapy.

Short Summary:
Lenalidomide and dexamethasone (Rd)-based triplets, in particular Daratumumab-Rd (DaraRd) and Carfilzomib-Rd (KRd), have been compared only by means of meta-analysis of randomized clinical trials (RCT). In the lack of RCT, our real-life propensity score matching comparison on lenalidomide sensitive MM patients treated in first relapse, showed better tolerability and prolonged PFS of DaraRd over KRd. In the rapidly changing scenario of emerging first line Daratumumab-based regimens, KRd still remains a valid salvage option.
INTRODUCTION

In the therapeutic scenario of multiple myeloma (MM) we have many biological drugs active as single agent as well as in different combinations: immunomodulatory drugs (IMIDs) like Lenalidomide (R) and Pomalidomide (P), anti-CD38 monoclonal antibodies (MoAb) such as Daratumumab (Dara) or Isatuximab (Isa), anti-SLAM7 MoAb Elotuzumab (Elo), new proteasome inhibitors (PI) such as Carfilzomib (K) and Ixazomib (Ixa). Despite the better outcome observed in the last decade with these new drugs, most patients with MM will relapse after first line therapy.(1-3)

Defining the better treatment algorithm at relapse, specifically in first relapse, still remains a therapeutical challenge, influenced by many factors, above all, by specific disease and patients’ characteristics, though drug availability and patients’ preference itself could affect this choice.(4, 5) Lenalidomide plus dexamethasone (Rd)-based triplet regimens (i.e., KRd, DaraRd, IxaRd, EloRd) have been approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of relapse refractory (RR) MM patients who have received at least one prior line of therapy, based on randomized phase 3 clinical trials (RCT).(6-9)

Following the principle of switch in drug class at relapse, Rd-based triplets, in particular DaraRd and KRd, have been indicated by recently updated European Society of Medical Oncology (ESMO) and International Myeloma Working Group (IMWG) guidelines as the preferred options in MM patients who have received frontline Bortezomib-based therapy without MoAb and who are not refractory to lenalidomide.(5, 10, 11)

Phase III RCT represents the optimal approach to assess the advantage of a specific regimen over another. So far there are no RCT that compare head-to-head these two different regimens. Network meta-analyses of data coming from trials that explored different Rd-based triplets, though with weaker grade of evidence with respect to RCT, showed better outcome with the combination of DaraRd over other Rd-based combinations, in particular KRd.(12-15)

Although there are some real-life surveys focusing on the efficacy and tolerability of different Rd-combinations outside RCT, no real-world studies were specifically focused on the first relapse scenario. (16-19)

Therefore, to clarify this issue from real-world data (RWD), we conducted a retrospective analysis on a series of MM patients in first relapse, treated in 12 Italian centers with the aim to describe the pattern of use of different Rd-triplet regimens outside clinical trials and to show whether DaraRd and KRd, indicated as standard of care in recently updated guidelines, represent the most common used regimens in clinical practice.(10, 11)
Afterwards, in the attempt to limit as much as possible the well-known limitations and bias of any retrospective observation, we used the propensity score method (PSM), a well-established approach to perform an adjusted comparison between two distinct treatment options, to create two cohorts, balanced for predefined covariates, and assess in a real-world scenario the relative efficacy and tolerability of DaraRd over KRd.(20-22)

METHODS

Study population and study design
After Ethic Committee approval of each participating center and patients’ consent to personal data processing, we review medical record of 430 MM patients in first relapse consecutively starting Rd-based triplets (DaraRd, KRd, IxaRd, EloRd) according to market-approved schedule between January 2017 and March 2021.(23-26) Patients primary refractory to first line treatment according to IMWG criteria were excluded from the study.(27)

Pattern of Rd-based triplets use
Data regarding Rd-based therapy distribution showed that the most common used regimen was DaraRd (54.4%, 234 patients), followed by KRd (34.6%, 149 patients). Treatment distribution change over time, as shown in Figure 1, with a progressive increase in the use of DaraRd. A limited number of patients received EloRd (8.4%, 36 patients) or IxaRd (2.6%, 11 patients), justifying the choice of focusing the comparison only on DaraRd and KRd groups.

Among patients treated with DaraRd and KRd, we found 66 patients (15%) addressed to salvage autologous stem cell transplantation (ASCT), 16 patients after DaraRd (24%) and 50 patients after KRd fixed induction (76%) (median PFS in transplanted patients 29.7 months).

Since transplant intensification was established to be a priori a significant bias of outcome, these patients in whom a salvage ASCT was originally planned, were excluded from the adjusted comparison.(28)

Statistical analysis and propensity score method
The outcome of DaraRd and KRd was compared using the propensity score (after a trimming of 5% of observations) to re-weight data, according to the Inverse Probability of Treatment method (IPTW analysis).(29) According to this method weights are assigned to patients based on the inverse of their probability (estimated by the propensity score) of receiving treatment. Result of this weighting assignment is the creation of a pseudo-population in which patients with a high probability of receiving treatment have a smaller weight and patients with a low probability of receiving treatment
have a larger weight. So, in this pseudo-population the distribution of patient characteristics used to calculate the propensity score are independent of treatment assignment.

Data captured for patients treated with DaraRd and KRd and selected as covariates for the propensity score calculation were the following: age at Rd-triplet starting, International Staging System (ISS) stage, presence of high-risk cytogenetic profile according to IMWG consensus, previous exposure to Bortezomib, previous ASCT, Very Good Partial Response (VGPR) or better, time between diagnosis and relapse, myeloma defining events at diagnosis.(27, 30-32)

The planned primary end point of comparison was progression-free survival (PFS).

Secondary end points were: a) overall response rate (ORR), b) VGPR or better, c) overall survival (OS), d) safety.

ORR accounts for partial response (PR) or better evaluated according to International Myeloma Working Group (IMWG) criteria.(27)

PFS was calculated from time of therapy start until the date of progression, relapse, death, or the date the patient was last known to be in response.

OS was calculated from the time of therapy start until the date of death for any cause or the date the patient was last known to be alive.

Grading of adverse events (AE) was evaluated by each clinician through Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.(33)

Qualitative variables were described as counts and percentages of each category. Quantitative variables have been summarized as median and Interquartile Range (IQR). Association between 2 qualitative variables was evaluated via Fisher’s exact test. Quantitative variables were compared between two groups by Mann-Whitney test.

Kaplan-Meier product limit method and Cox regression models (re-weighted for IPTW) were used to estimate OS and PFS and to compare them between triplets. A landmark analysis was carried out to compare PFS of DaraRd vs KRd according to the 6-months response (≥VGPR vs PR). Results from Cox models were reported in terms of Hazard Ratio (HR) (KRd: reference group) for the comparison of DaraRd vs KRd with 95% Confidence Interval (95%CI).

Best response, administration and safety were compared between triplets by logistic regression model (re-weighted for IPTW) and results were reported in terms of Odds Ratio (OR) for the comparison of DaraRd vs KRd (reference group) with its 95%CI. Reason for treatment discontinuation was compared between triplets by multinomial logistic regression (re-weighted for IPTW), and results were reported as Relative Risk-Ratios (RRR) for the comparison of DaraRd vs KRd (reference group) with 95%CI. P-values lower than 0.05 were considered significant. All
statistical analyses were performed using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.)

RESULTS

Comparison between DaraRd and KRd cohorts

The adjusted comparison was performed on three hundred and sixteen patients, 217 receiving DaraRd regimen, compared with 99 treated with KRd.

The unmatched comparison of baseline characteristics in two groups showed that they were well-balanced, except for few differences (Table 1). In details, patients addressed to DaraRd were slightly older (median age was 69 years vs 64 years in KRd, p<0.001), and they had received a lower rate of prior ASCT (54.4% vs 71.7% in KRd, p= 0.004). Nearly all patients had received prior Bortezomib, few patients in both groups were previously exposed to lenalidomide (12 patients, 3.8%), carfilzomib (8 patients, 2.5%) or Daratumumab (1 patients, 0.3%). Most patients in both groups started salvage therapy for symptomatic relapse (93.5% in DaraRd and 99% in KRd).

The cytogenetic profile was evaluable in 61% of DaraRd pts and in 72% of KRd pts. Rate of patients carrying one or more high-risk cytogenetic abnormalities, including deletion (17p), translocation (4;14) and translocation (14;16), detected by fluorescence in situ hybridization (FISH) were similar in both groups (26% in DaraRd vs 30% in KRd, p>0.90).

Comparison between DaraRd and KRd administration

The median follow-up of the entire cohort was 22.8 months (range 10.8-32.4 months), although this varies by treatment group (median follow-up for DaraRd 19 months vs 40 months for KRd, p<0.001). There was no difference in terms of median number of administered cycles between DaraRd and KRd group [13 (range 6-21) vs 10 (range 6-18)] (IPTW analysis: OR: 0.1 (0.0-0.3), p=0.105). Discontinuation rate was significantly lower in DaraRd in comparison to KRd [25.8% (56 patients) vs 58.6% (58 patients)] (IPTW analysis: OR: 0.2 (0.2-0.3), p<0.001). Most common reason for treatment discontinuation was progressive disease (PD) [31 patients (14.6%) in DaraRd and 34 patients in KRd (34.3%)] followed by adverse events [18 patients (8.5%) in DaraRd and 17 patients (17.1%) in KRd], a limited number of patients in both groups stopped treatment for other reasons [7 patients (3.3%) in DaraRd and 7 patients (7%) in KRd]. Multinomial logistic regression (re-weighted for IPTW) showed that patients treated with DaraRd are less likely than patients treated with KRd to discontinue treatment for AEs rather than for progressive disease (IPTW analysis: RRR=0.4 (0.2-0.8), p=0.014)
Efficacy of DaraRd and KRd

The median time to best response was similar between DaraRd and KRd (5.5 months vs 4.8 months, p=0.670). No significant difference was found between DaraRd and KRd in terms of best response achieved (Table 2), both in the comparison of ORR (IPTW analysis: OR=0.9, p=0.685) and when comparing the rate of CR (IPTW analysis: OR=1.2, p=0.360) and the rate of VGPR or better (IPTW analysis: OR=0.9, p=0.582).

Adjusted median PFS was longer for patients addressed to DaraRd when compared to KRd (29.8 months vs 22.5 months; IPTW analysis: HR=0.7, 95%CI: 0.6-1.0, p=0.028) (Figure 2).

In a landmark analysis of PFS by 6-months response, in patients reaching VGPR or better, PFS was prolonged with DaraRd [24-months PFS for DaraRd was 91.8% (95%CI: 86.0-95.2%) vs 69.7% (95%CI: 59.3%-77.9%) for KRd (IPTW analysis: HR: 0.5, 95%CI: 0.3-0.8, p=0.007)]. Patients with PR had similar PFS [24-months PFS for DaraRd was 27.3% (95%CI: 16.4-39.4%) vs 14.0% (95%CI: 1.8-38.3%) in KRd (IPTW analysis: HR: 0.8, 95% CI: 0.4-1.5, p=0.481)] (Figure 3).

By the cut-off date, 78 patients (24.7%) had died, mainly for disease-related causes (56 patients, 72%). OS did not differ according to Rd-triplet (24-months OS in DaraRd 100% vs 98.1% in KRd, IPTW analysis: HR=0.9, 95%CI: 0.6-1.2, p=0.377) (Figure 4).

Safety of DaraRd and KRd regimens

The most common reported AEs were hematologic toxicity and infections. Overall, 3 patients died while on treatment: two patients during DaraRd for pneumonia, one patient during KRd for sepsis. Hematological toxicity (all grades) was similar between groups (IPTW analysis: OR=0.7, 95%CI: 0.4-1.1, p=0.102). No difference was found also in terms of grade 3 and 4 hematological AEs (IPTW analysis: OR=0.7, 95%CI: 0.4-1.1, p=0.102). Table 4 shows a summary of non-hematological toxicity. When considering non-hematological side effects, DaraRd was better tolerated, with a lower incidence of all grade AEs (IPTW analysis: OR=0.4, 95%CI: 0.3-0.6, p<0.001). The lower toxicity rate with DaraRd was confirmed even when considering grade 3 and 4 non hematological AEs (IPTW analysis: OR=0.4, 95%CI: 0.3-0.7, p<0.001). Incidence of grade 3 and 4 infections was 9.7% during DaraRd and 13.1% with KRd. Regarding cardiovascular toxicity, in patients receiving KRd cardiac grade 3 and 4 AEs were observed in 12.2% of the entire cohort: 5 patients had grade ≥3 hypertension, 7 patients suffered for grade ≥3 cardiac events (i.e., arrhythmia, ischemic heart disease, congestive heart failure).
DISCUSSION

ESMO and IMWG guidelines recommend the use of Rd-based triplets, in particular of DaraRd and KRd, for the treatment of first relapse lenalidomide sensitive MM patients, based on the results of phase 3 RCT ASPIRE and POLLUX. These studies showed superior outcome for triplet regimens with respect to doublets.(6-11)

Although randomized phase 3 trials remains the optimal approach to inform the superiority of a treatment over another, there are no RCT comparing these regimens head-to-head in homogenous populations.

Some network meta-analyses of RCT provided indirect comparison, suggesting that anti-CD38 MoAb-based combinations give better outcome.(14, 15)

In addition, given the stringent criteria for patient-selection in clinical studies, evidences from real-world experiences are also useful to explore the pattern of use, the efficacy and the safety of Rd-triplets in daily practice.(34)

Beside some interconnected variables that influenced treatment decision at relapse (peculiar clinical aspects, pattern or relapse, previous therapeutic history), there are additional factors that could limit real-life decisions making process. Among them, timing of market approval and local drug availability are the most relevant.(35)

In Italy, the first triplet that received market approval was KRd, followed by EloRd, and after few months, DaraRd and IxaRd, this latest with a specific restriction for cytogenetically defined high-risk patients when used in first relapse.(23-26)

Therefore, we depicted the different use of Lenalidomide based-triplets in a large cohort of 430 MM patients treated in 12 Italian centers in a time-frame lasting from January 2017 to March 2021.

In our study, DaraRd resulted the treatment of choice in more than half patients (54.4%) with a time dependent increase in prescription, followed by KRd (34.6%). EloRd and IxaRd were used, as expected, in much smaller groups (Figure 1). This pattern of utilization reflects the progressive change in prescription limitations as well as the acknowledgement for better hazard ratio and longer PFS emerging from extended follow-up of RCT.(36, 37)

Still focusing on treatment distribution, we found that salvage ASCT after a fixed number of Rd-based cycles, is still an option for selected patients, as suggested by ESMO and IMWG guidelines.(10, 28)

ASCT was administered in 66 patients (15%), more commonly after KRd triplet re-induction (50 patients, 76%). Since transplant intensification could represent a significant bias for the outcome, we excluded transplanted patients from subsequent DaraRd vs KRd comparison.
Nowadays, there are growing experiences confirming the efficacy of KRd salvage regimen when used in daily practice.\textsuperscript{(18, 19, 38)}

Collection of data regarding anti-CD38 MoAb Daratumumab are more limited, often focusing on its use as single agent in more advance RRMM patients.\textsuperscript{(39, 40)}

The few RWD on DaraRd found gaps in terms of response rate and PFS with respect to POLLUX trial, largely attributed to higher rate of baseline adverse prognostic factors like multiple comorbidities, advanced disease phases, lenalidomide refractoriness.\textsuperscript{(16, 41)}

The population of our study had some homogeneous baseline characteristics (all patients were treated in first relapse, they were not primary refractory, and were mostly lenalidomide naïve), that could represent the clinical setting for better evaluating the real-life performances of DaraRd as well as KRd, and partly helps in limiting the well-known persistent bias of a retrospective analysis.\textsuperscript{(10)}

The adoption of the propensity score matched analysis, partly reduces the limits of our non-randomized retrospective comparison by balancing for the several differences in baseline patients’ characteristics.\textsuperscript{(29)}

Most of the covariates that we set up for our matching analysis (age at Rd-triplet starting, high-risk cytogenetic profile, ISS stage, previous transplant, good response at first line therapy, time between diagnosis and relapse) are known confounders that significantly impact on PFS. The availability of these data in a significant part of our population help us to mitigate the loss of patients entering the pseudo population evaluable for the comparison itself.

In terms of efficacy, new triplet regimens have substantially increased the probability of achieving good quality response, in particular CR, this factor has been associated with better outcome irrespective of type of therapy and disease phase.\textsuperscript{(42, 43)}

In our matched comparison, most patients achieved at least partial response, without significant difference between DaraRd and KRd (OR=0.9 (0.5-1.6), p=0.685). In addition a significant proportion of patients reached good quality response, with similar rates of at least VGPR (OR=0.9 (0.6-1.3), p=0.582), and CR or better (OR=1.2 (0.8-1.9), p=0.360). On average efficacy was superimposable to that coming from ASPIRE (KRd vs Rd) and POLLUX (DaraRd vs Rd) trials.\textsuperscript{(6, 7)}

Regarding the outcome, we found that the median PFS with DaraRd was 29.8 months, better than that reported by Antonioli and Davies, and longer with respect to PFS observed in our KRd group (median PFS 22.5 months).\textsuperscript{(16, 41)}
In a landmark analysis of PFS by 6-months response, the advantage of DaraRd over KRd was also confirmed in patients reaching VGPR or better, while was lost in the smaller fraction of patients (cfr Figure 3) with a PR.

In any case, the outcome emerging in both cohorts is worse than that reported in RCT, especially for DaraRd. In fact, in POLLUX sub-analysis, patients in first relapse had a median PFS of 53.3 months, while in ASPIRE the median PFS in first relapse was 29.6 months.(6, 36)

One of the reasons probably explaining for the general loss of performances in our real-world setting is the limited number of cycles received, either with DaraRd (13 cycles) or with KRd (10 cycles). Duration of active treatment in our study was comparable to RWD, but definitely lower than RCT, where the median duration of therapy was 34.3 months in POLLUX and 22 months in ASPIRE, with a progressive gain in response and PFS as long as patients stayed on continuous treatment.(6, 7, 16, 18, 19, 36, 41)

In addition, some baseline characteristics may have influenced the general outcome in daily practice, partly explaining the gap between our RWD and RCT. Among relevant prognostic parameters, negative impact of high-risk cytogenetic has been improved, but not completely abrogated even by the most effective regimens employed, including DaraRd and KRd. In detail subgroup analysis of POLLUX and ASPIRE showed that the differences in terms of PFS of these two regimens when used in high-risk defined patients, is much more limited (26.8 months for DaraRd and 23.1 months for KRD).(44, 45)

One third of our patients in both DaraRd and KRd cohorts were harboring high-risk features while the rate of these patients in POLLUX and ASPIRE were lower (15.4% and 12.1%), maybe contributing to the loss of performance of both regimens in our study; nevertheless the specific impact of high risk FISH should be addressed only by specific ad hoc studies. (41, 45)

Age, as well as some age-linked comorbidities, most of all cardiovascular disease, maintained its negative impact even in the novel agent era; given the general increase in elderly patients, treatment choice in clinical practice is largely influenced by the tolerability of a specific treatment.(46)

KRd is effective in elderly patients albeit at the cost of higher toxicity, most of all, in terms of hypertension and cardiac events.(47) Even if some loss of DaraRd performances were observed in elderly patients (median PFS in the subgroup of POLLUX with \( \geq \) 75 years, 28.9 months), its safety profile remains acceptable regardless of age.(7, 48, 49)

The rapid and remarkable increase over time in the use of DaraRd may be linked to its higher tolerability even when used in a generally older population (Figure 1 and Table 1). Details regarding treatment discontinuation and safety analysis confirmed that DaraRd is quite always well-tolerated also in our real-life scenario. In fact, focusing on treatment received, we observed a lower
discontinuation rate with DaraRd (25.8% vs 58.6%, p<0.001), with a relative risk ratio of discontinuation for progression rather than for toxicity for DaraRd vs KRd (RRR=0.4, p=0.014). Regarding toxicity, rate of grade 3-4 non-hematological AEs was significantly lower with DaraRd (Table 4).

Anyway, since in our study patients addressed to KRd are on average younger, grade 3 and 4 toxicity, in particular cardiovascular AEs, were superimposable to ASPIRE and to previously RWD.(6, 18, 19)

In conclusion, our real-world data depict an evolving pattern in the daily management of lenalidomide sensitive MM patients in first relapse, with a progressive increase in the last few years in the use of DaraRd. Taking into account the limits of any analysis gathered from retrospective observation, our real-life matching comparison showed higher tolerability of DaraRd over KRd, without new emerging safety concerns for both regimens. In the lack of RCT that directly compare these triplet regimens, our real life experience suggests a prolonged PFS with DaraRd over KRd, when used in patients who relapsed after primary therapy not including lenalidomide. KRd, thanks to its confirmed efficacy in terms of good response rate, can be a valid alternative option for fit patients in daily practice, taking into account the emerging scenario of Dara-exposed patients. (5, 48, 50)

All these findings suggest to tailor the management of our daily practice, balancing the best efficacy with the higher tolerability.
References


41. Davies F, Rifkin R, Costello C, et al. Real-world comparative effectiveness of triplets containing bortezomib (B), carfilzomib (C), daratumumab (D), or ixazomib (I) in relapsed/refractory multiple myeloma (RRMM) in the US. Ann Hematol. 2021;100(9):2325-2337.


**Table 1** – Baseline characteristics of KRd and DaraRd treated patients in the original cohorts and after IPTW analysis

<table>
<thead>
<tr>
<th>Type of Treatment at relapse</th>
<th>ORIGINAL COHORTS</th>
<th>PSEUDO-POPULATION (IPTW analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRd (N=99)</td>
<td>DaraRd (N=217)</td>
</tr>
<tr>
<td><strong>Myeloma defining events at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Any <strong>CRAB</strong> criteria - N (%)</td>
<td>94 (94.9%)</td>
<td>202 (93.1%)</td>
</tr>
<tr>
<td>o HyperCalcemia</td>
<td>22 (22.2%)</td>
<td>34 (15.7%)</td>
</tr>
<tr>
<td>o Renal failure</td>
<td>24 (24.2%)</td>
<td>61 (28.2%)</td>
</tr>
<tr>
<td>o Anemia</td>
<td>55 (55.6%)</td>
<td>121 (56.0%)</td>
</tr>
<tr>
<td>o Bone lesions</td>
<td>81 (81.8%)</td>
<td>158 (73.2%)</td>
</tr>
<tr>
<td>• Only <strong>SLiM</strong> CRAB criteria - N (%)</td>
<td>5 (5.1%)</td>
<td>15 (6.9%)</td>
</tr>
<tr>
<td><strong>ISS - N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stage II and III</td>
<td>59 (63.4%)</td>
<td>129 (64.5%)</td>
</tr>
<tr>
<td><strong>First Line treatment – N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ASCT in first line</td>
<td>71 (71.7%)</td>
<td>118 (54.4%)</td>
</tr>
<tr>
<td>• PI-based therapy</td>
<td>96 (97.0%)</td>
<td>207 (95.4%)</td>
</tr>
<tr>
<td><strong>Good quality response during first line - N (%)</strong></td>
<td>69 (69.7%)</td>
<td>146 (68.5%)</td>
</tr>
<tr>
<td>• ≥VGPR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time from diagnosis and relapse - Mean (SD)</strong></td>
<td>2.9 (2.2)</td>
<td>3.4 (2.7)</td>
</tr>
<tr>
<td><strong>Median age at second line start - Mean (SD)</strong></td>
<td>64 (8)</td>
<td>69 (9)</td>
</tr>
<tr>
<td><strong>CYTOGENETIC profile at relapse – N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Missing</td>
<td>28 (28%)</td>
<td>80 (39%)</td>
</tr>
<tr>
<td>• Evaluate</td>
<td>71 (72%)</td>
<td>137 (61%)</td>
</tr>
<tr>
<td>o Standard</td>
<td>41 (42%)</td>
<td>79 (35%)</td>
</tr>
<tr>
<td>o High riskb</td>
<td>30 (30%)</td>
<td>58 (26%)</td>
</tr>
</tbody>
</table>

Abbreviations: KRd, carfilzomib-lenalidomide-dexamethasone; DaraRd, daratumumab-lenalidomide-dexamethasone; IPTW, inverse probability of treatment weighted; N, number; ISS, International Staging System; ASCT, Autologous Stem Cell Transplantation; PI, Proteasome Inhibitor; VGPR, Very Good Partial Response; SD, Standard Deviation

a (S) 60% or more clonal plasma cells detected in the bone marrow, (Li) Light chains and (M) MRI
b High risk cytogenetic profile was identified by fluorescence in situ Hybridation according to IMWG consensus(30)
**Table 2** - Summary of best response achieved in DaraRd and KRd cohorts

<table>
<thead>
<tr>
<th>Best overall response&lt;sup&gt;a&lt;/sup&gt; – N (%)</th>
<th>ORIGINAL COHORTS</th>
<th>IPTW analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DaraRd (N=211)</td>
<td>KRd (N=98)</td>
</tr>
<tr>
<td>CR or better</td>
<td>47 (22.2%)</td>
<td>26 (26.6%)</td>
</tr>
<tr>
<td>• sCR</td>
<td>8 (3.7%)</td>
<td>8 (8.2%)</td>
</tr>
<tr>
<td>• CR</td>
<td>39 (18.5%)</td>
<td>18 (18.4%)</td>
</tr>
<tr>
<td>VGPR or better</td>
<td>133 (63%)</td>
<td>64 (64.4%)</td>
</tr>
<tr>
<td>• VGPR</td>
<td>86 (40.8%)</td>
<td>38 (37.8%)</td>
</tr>
<tr>
<td>• PR</td>
<td>60 (28.4%)</td>
<td>22 (22.5%)</td>
</tr>
<tr>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>193 (91.5%)</td>
<td>85 (86.7%)</td>
</tr>
<tr>
<td>SD and PD</td>
<td>18 (8.6%)</td>
<td>13 (13.2%)</td>
</tr>
</tbody>
</table>

Abbreviations: DaraRd, daratumumab-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; IPTW, inverse probability of treatment weighted; N, number; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, Overall response rate; OR, Odds Ratio; 95%CI: 95% a Confidence Interval<sup>a</sup> Best response assessment by physician according to International Myeloma Working Group criteria(27) <sup>b</sup> ORR include ≥PR

**Table 3** - Non-hematological Adverse Event (all grades and grade ≥ 3) in DaraRd and KRd cohorts

<table>
<thead>
<tr>
<th>Adverse Event – N (%)</th>
<th>All Grades</th>
<th>≥ Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DaraRd (N=217)</td>
<td>KRd (N=99)</td>
</tr>
<tr>
<td>o Infections</td>
<td>60 (27.7%)</td>
<td>35 (35.4%)</td>
</tr>
<tr>
<td>o Gastrointestinal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41 (18.9%)</td>
<td>18 (18.2%)</td>
</tr>
<tr>
<td>o Fatigue</td>
<td>21 (9.7%)</td>
<td>12 (12.1%)</td>
</tr>
<tr>
<td>o Deep Vein Thrombosis</td>
<td>9 (4.2%)</td>
<td>10 (10.1%)</td>
</tr>
<tr>
<td>o Rash</td>
<td>9 (4.2%)</td>
<td>7 (7.1%)</td>
</tr>
<tr>
<td>o Peripheral Neuropathy</td>
<td>9 (4.2%)</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>o Hepatic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (0.9%)</td>
<td>4 (4.0%)</td>
</tr>
<tr>
<td>o Acute Renal Failure</td>
<td>2 (0.9%)</td>
<td>3 (3.0%)</td>
</tr>
</tbody>
</table>

**Adverse Event of Specific interest – N (%)**

<table>
<thead>
<tr>
<th></th>
<th>DaraRd (N=217)</th>
<th>KRd (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Cardiac&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4 (1.8%)</td>
<td>12 (12.1%)</td>
</tr>
<tr>
<td>o Hypertension</td>
<td>5 (2.3%)</td>
<td>8 (8.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: DaraRd, daratumumab-lenalidomide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; N, number
<sup>a</sup> Gastrointestinal include diarrhea, constipation and abdominal discomfort
<sup>b</sup> Hepatic include abnormality in hepatic laboratory tests
<sup>c</sup> Cardiac include arrhythmia, ischemic heart disease, congestive heart failure

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Figure legends

**Figure 1** - Pattern of Rd-based triplet distribution overtime

**Figure 2** - Progression-free survival of patients treated with DaraRd *versus* KRd after cohorts matching

**Figure 3** - Six-months landmark analysis of progression-free survival after cohorts matching according to therapy received (DaraRd *versus* KRd) and response achieved

**Figure 4** - Overall survival of patients treated with DaraRd *versus* KRd after cohorts matching