line treatment. The proportion of patients not receiving a subsequent line of therapy due to death is also summarized by lines of therapy in **Table 2.**
Summary/Conclusion: A substantial number of patients with NDMM who are transplant eligible did not receive subsequent lines of therapy, with attrition by lines of therapy ranging from 23–40%. The increase in attrition rates with each additional line of therapy underscores the need to utilize upfront therapy associated with optimal progression-free survival. Further studies evaluating the etiologic basis for this unexpectedly high attrition rate are warranted.

Table 1: Baseline characteristics

Variables	Mean (SD) /N (%)
Age at MM diagnosis, Y	61.7 (8.8)
Male, n (%)	940 (58.8)
Race, n (%)*	
White/Caucasian	678 (75.3)
African American	50 (5.6)
Asian	12 (1.3)
Black	79 (8.8)
Hispanic	5 (0.6)
Unknown/other	76 (7.3)
Comorbidities	
Cardiac arrhythmia	244 (15.3)
Congestive heart failure	106 (6.6)
Hypertension, complicated	214 (13.4)
Hypertension, simple	902 (56.4)
Hepatic disease	127 (7.9)
Pulmonary disease	64 (4)
Renal impairment	402 (25.1)
Valvular disease	196 (12.2)

*Race data not available in the OPTUM™ Commercial Claims database.

Table 2: Attrition rates by line of therapy

LOT	Frequency	% Attrition	Deaths, N (%)	No subsequent treatment, N (%)	Mean treatment duration Months – SD (median)
1	1599	-	125 (8)	235 (14.7)	5.9 ±6.9 (4.2)
2	1239	23	146 (12)	221 (17.8)	5.2 ±7.7 (2.5)
3	872	30	117 (13)	223 (25.6)	7.1 ±9.8 (3.2)
4	532	39	78 (15)	137 (25.8)	6 ±8 (3.2)
5	317	40	74 (23)	76 (24.0)	4.9 ±5.9 (2.7)

PF644 CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: THE REAL LIFE EXPERIENCE OF RETE EMATOLOGICA PUGLIESE (REP)

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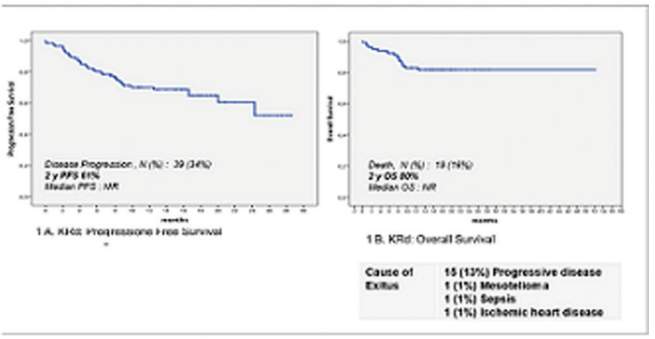
Background: Carfilzomib, lenalidomide and dexamethasone (KRd) has been approved for the treatment of relapsed and refractory multiple myeloma (RRMM) based on ASPIRE clinical trial. However, its effectiveness and safety profile in real clinical practice should be further assessed.
Aims: We retrospectively evaluated 120 consecutive RRMM patients treated with KRd, in 9 hematology departments of Rete Ematologica Pugliese (REP), with the aim to evaluate the efficacy and safety with KRd treatment in a real world setting.
Methods: Between December of 2015 and August 2018,120 RRMM patients were analyzed.The patients' baseline characteristics are presented in Table 1. Median patient's age was 66 years and 41 patients(34%) were older than 70 years. The median number of previous treatment lines was 1 (range 1–11). The 94% of the patients had been already treated with bortezomib-based regimens and 33% with both lenalidomide- and bortezomib-based regimens. Moreover, half of the patients (52%) had a previous autologous stem cell transplant. The median time from the diagnosis to start of treatment with KRd was 40 months (range 5–295) and 30 patients were treated with KRd early (≤18 months from diagnosis).Disease status at the start of treatment with KRd was refractory in 33 patients(29%) and 13 patients(12%) were refractory to lenalidomide. Twenty-four patients(21%) were refractory at last therapy before KRd enrollment.
Results: The overall response rate (ORR) was 84%(n = 93),with 23%(25) complete response (CR) and 50%(55) very good partial response(VGPR).The median duration of response was 12,9 months (range, 3,33–27,7). ORR was higher in patients relapsed after a previous autologous transplant (ASCT;56% vs 37% in those relapsed without prior ASCT;p 0,05).Patients treated in late relapse had a better ORR (44%) vs those in early relapse (19%; p 0,02). After a median follow-up of 13,4 months, median PFS was not reached (NR) and 2y-PFS was 61%, Figure 1. PFS was longer in responding patients (achieving at least PR) to those with less than PR (median PFS NR vs 4,9 months;p 0,0001).Median PFS in patients relapsed after a prior ASCT was NR vs 20 months in those without prior ASCT, (p 0,002).Patients achieving ASCT after KRD had a better PFS in confront to those without ASCT (median NR vs 9 months, p 0,001).Several baseline patient characteristics, such as the III ISS scoring, older age, prior exposure to lenalidomide and early relapse were found to negatively impact PFS.Twenty-eight patients(24%) performed 4 KRd cycles as bridge treatment to ASCT. The 64% of patients reached a VGPR and 67% received ASCT, with 9 upgraded from VGPR to complete response (CR) after ASCT.The treatment discontinuation rate due to adverse events (AEs) was 13%, most commonly related to lenalidomide(8%). KRd dose reduction was necessary in 11% of patients (2,5% for carfilzomib and 8% for lenalidomide).The most frequent AE was neutropenia(43%) and anemia (41%). Infections occurred in 10% of patients.Adverse Cardiovascular toxicity (Atrial fibrillation and pulmonary hypertension)occurred in 8% of patients.

Table 1. Patients' baseline characteristics and details of the previous therapies

	N= 120
Median age, years (range)	66 (34-81)
Age ≥ 70 years, n (%)	41 (34)
III ISS disease staging, n (%)	50 (44)
Extramidollar disease, n (%)	13 (11)
Cytogenetic profile, n (%)	
Unkwown	77 (64)
Standard Risk	35 (29)
High Risk	8 (7)
Elevated LDH, n (%)	51 (46)
Median Time since initial therapy, months (range)	40 (5-295)
≤ 18 months	30 (25)
Median number of previous lines of therapy (range)	1 (1-11)
Number of previous lines of therapy, n (%)	
2 / ≥ 3	24 (20) / 33 (29)
Previous autologous transplant, n (%)	62 (52)
Previous allogeneic transplant, n (%)	6 (5)
Previous therapy, n (%)	
Bortezomib / Lenalidomide	113 (94) / 41 (34)
Bortezomib and Lenalidomide	39 (33)
Pomalidomide / Monoclonal Antibodies	8 (7) / 3 (2)
Refractory, n (%)	33 (29)
Bortezomib	18 (16)
Lenalidomide	11 (10)
Bortezomib and Lenalidomide	2 (2)
Refractory to last therapy, n (%)	24 (21)

Figure 1. Progression Free Survival (1A) and Overall Survival (1B)



Summary/Conclusion: Our analysis confirmed that KRd is effective in RRMM patients. It is well tolerated and applicable to the majority of patients outside clinical trials. A longer PFS was shown in patients

achieving at least a partial response (PR), relapsing after previous ASCT and in those with the possibility to perform ASCT after KRd treatment. Accordingly,KRd should be used as an optimal bridge regimen to ASCT. Previous ASCT should not hamper the option for KRd therapy.

PF645 EXPOSURE-RESPONSE ANALYSIS & DISEASE MODELING FOR SELECTION OF OPTIMAL DOSING REGIMEN OF ISATUXIMAB AS SINGLE AGENT IN PATIENTS WITH MULTIPLE MYELOMA

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Background: Isatuximab is an anti-CD38 monoclonal antibody with multiple modes of action for killing tumor cells through direct tumor targeting and immune cell engagement [1].
Aims: Exposure-Response (E-R) analysis and disease modelling of tumor burden were performed to evaluate the relationship between isatuximab exposure and efficacy outcome and to support dosing regimen selection for isatuximab as a single agent in relapsed/refractory multiple myeloma (RRMM) patients.
Methods: The E-R analyses were conducted in 194 RRMM patients evaluable for pharmacokinetics (PK) from two monotherapy trials, a phase 1/2 trial (NCT01084252)[2] and a phase 1 trial (NCT02514668). Isatuximab was administered intravenously at doses from 1 to 20 mg/kg once a week or every 2 weeks. Several isatuximab exposure parameters were tested and their association with the probability of achieving an objective response (CR, VGPR or PR) was examined by logistic regression modeling. Baseline covariates were also considered in the model to reduce their potential confounding effects. Disease progression was captured in a subset of 122 evaluable patients with the dynamics of the serum M-protein and accounted for dropout using a joint model. Trial simulations were then performed to evaluate different dosing regimens of interest using both models.
Results: The E-R relationship was best described by Emax model, in which Ctrough at 4 weeks and percent of bone marrow plasma cells were significant predictors of overall response rate (ORR). Patients with bone marrow plasma cells lower than 50% were more likely to respond. For a given bone marrow plasma cell value, higher probability of response to treatment was obtained with higher Ctrough at 4 weeks. Longitudinal data of M-protein was adequately described by a tumor growth inhibition model [3,4] and provided more insights into the response of patients over time. Therefore, a high loading dose of 20 mg/kg weekly over 4 weeks was chosen for maximizing the tumor response and a maintenance dose of 20 mg/kg every 2 weeks appeared sufficient to sustain efficacy. Clinical trial simulation demonstrated that this dosing regimen presented a probability of success of 76% to reach 30% ORR (5,000 trials with 100 patients) and would allow 52% reduction of serum M-protein from baseline at 2 months of treatment. In addition, isatuximab appeared to be well tolerated at this dose level.
Summary/Conclusion: Model-based drug development has been successfully applied to support phase II isatuximab monotherapy dosing regimen selection in RRMM patients. This approach increases both the robustness of dose selection decision making and the chances of success for future clinical trials.
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PF646 ASSOCIATION BETWEEN BORTEZOMIB CUMULATIVE DOSE AND TREATMENT-FREE INTERVAL IN TRANSPLANT-INELIGIBLE PATIENTS WITH PREVIOUSLY UNTREATED MULTIPLE MYELOMA

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Background: The phase III VISTA study has demonstrated that bortezomib-melphalan-prednisone (VMP) leads to improved clinical outcomes, such as significant improvement of overall survival (OS) for patients with myeloma who are ineligible for stem cell transplantation, in comparison with melphalan-prednisone (MP) (San Miguel et al, J Clin Oncol, 3:448–455, 2013). It was demonstrated a higher cumulative bortezomib dose is associated with improved OS (Mateos MV et al, Am J Hematol 90:314–319, 2015). Treatment-free interval (TFI) is another important clinical outcome measure proposed by ASCO and ESMO Draft Value Frameworks for neoplastic drugs (Becker DJ et al, J Oncol Practice, 13:e753-e665, 2017; Richardson P et al, Expert Review of Hematology 10:933–939, 2017). However, it is not known whether higher cumulative bortezomib doses are associated with a prolonged TFI.
Aims: To determine whether a higher cumulative bortezomib dose (obtained by longer treatment duration, more intensive therapy or both) is associated with longer TFI, or lower cumulative incidence of subsequent therapy.
Methods: This is a post hoc analysis of the patients treated with VMP in the VISTA randomized clinical trial with the data cut of 2008. Baseline characteristics and clinical outcome (TFI, defined as time from the last dose of study drug to the start of subsequent treatment) were analysed in two groups based on median cumulative bortezomib dose. For subjects who were not known to have died, survival time was censored at the date last known to be alive. Multivariate competing risks hazard ratios (HR), as well as estimates of cumulative incidence (CI) of subsequent therapy, were computed using the Fine and Gray proportional hazards (PH) model for sub-distributions. HR <1 is in favour of higher bortezomib cumulative group.
Results: The median cumulative dose of bortezomib was 39 mg/m^2. The median follow-up was 25.9 months. Patients in the higher cumulative bortezomib dose group (n = 170) were significant younger (70.8 ± 4.6 vs. 73.6 ± 6.2, $P < 0.0001$) than the lower group (n = 170). No major differences between groups are identified in respect of gender, ISS, type of myeloma, ECOG, cytogenetic risk, and baseline creatinine clearance. Only 44 (25.9%) and 24 (4.1%) patients in the lower and higher dose group had documented subsequent therapy, respectively. Overall, 39 (22.9 %) and 10 (5.9%) patients died in lower and higher dose group, respectively. TFI did not reach the median for either dose group, though it was significantly longer in the higher (≥39 mg/m^2) versus lower (<39 mg/m^2) cumulative bortezomib dose group, with HR as 0.48 (P = 0.004) and age-adjusted HR as 0.49 (P = 0.009). The CI at month 12 for subsequent therapy was 0.134 for the higher dose group vs. 0.258 for the lower dose group (Figure 1).