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Authors contribution

KLH, HG and AJV conceived and designed the work, collected clinical data, interpreted the results, wrote the manuscript and approved the final version; AGS established the Redcap database, collected clinical data, interpreted the results, revised the manuscript and approved the final version, TWK performed all statistical analysis, interpreted the results, revised the manuscript and approved the final version, MBL/CH/EH/STB/KN/KFI/EMT/MD/EK/CS collected clinical data, interpreted the results, revised the manuscript and approved the final version, BP/MFB/LMRG/EK/MKA collected cytogenetic data, interpreted the results, revised the manuscript and approved the final version.

Abstract

Real world evidence is important since most patients cannot be included in randomized clinical trials (RCT). In a nationwide, cohort of relapsed/refractory multiple myeloma patients treated with daratumumab (N= 635), we retrospective studied patients treated with carfilzomib (N=251). Data were collected by audit of medical records. We compared characteristics of patients treated with carfilzomib before daratumumab (Car-Da; N=150) and after daratumumab (Da-Car; N=101) with those not treated with carfilzomib (N=384). Furthermore, we examined effectiveness and safety of carfilzomib..

The group of patients treated with carfilzomib differed from patients not treated with carfilzomib in the following parameters: They were younger, more were treated up-front with high dose melphalan and autologous stem cell transplantation (HDM-ASCT)and had relapse within 18 months thereafter, and more had high-risk cytogenetic abnormalities (CA) and amplification 1q (amp1q). In patients treated with Car-Da, 30.3% had high-risk CA and 30.1% had amp1q and in Da-Car it was 43.3% and 41%, respectively. In the Car-Da cohort, 34.4% experienced early relapse after HDM-ASCT versus 47.4% in the Da-Car cohort. The percentage of patients with very good partial remission was higher in patients treated with Car-Da compared to Da-Car (31.7% versus 17.4%). The median duration of treatment and time to next treatment (TNT) of Car-Da/Da-Car were 4.6/4.3 months and 7.1/4.3 months and only a trend toward superior TNT for Car-Da was found (p=0.06). Toxicity of carfilzomib was the same as reported in RCT. A similar poor TNT of daratumumab was found when used before (5.6 months) or after carfilzomib (4.9 months).

In this cohort of patients with sequential treatment with carfilzomib and daratumumab or vice versa, a high percentage of patients were high-risk by CA, amp1q, and early relapse after HDM-

ASCT. Outcome of Car-DA and outcome of Da-Car were equally poor. These patients should be considered for new promising treatment strategies.

Introduction

Outcome of treatment in the real-world setting is becoming increasingly important as several analyses of have shown that randomized clinical trials (RCTs) only include 10-30% of all multiple myeloma (MM) patients (1-3). Furthermore, studies imply that high risk patients are more prevalent in real-life (4, 5). MM patients not fulfilling the criteria for RCT have shorter survival in part explained by worse performance status, older age, and more co-morbidity (6). Another explanation for patients not being included in RCT is screening failure due to aggressive disease with progression that requires immediate intervention. Aggressive disease is defined by high-risk cytogenetic abnormalities (CA), such as t(4;14), t(14;16), del17p, and amp1q, early relapse after up-front treatment with high-dose melphalan with autologous stem cell transplantation (HDM-ASCT) and survival below 24 months in the era of novel agents (7-15). Retrospective observational studies can help us fill the gap of knowledge between RCTs and real-world practice.

The aim of this study was to describe a population of RRMM patients treated with carfilzomib either before or after treatment with daratumumab in a national real-world setting. Carfilzomib was approved in Denmark in November 2015 and daratumumab in October 2016. By including patients treated with carfilzomib and daratumumab within in a short time frame, we included patients with early relapse after either daratumumab or carfilzomib. We present the characteristics of these patients with poor outcome. Furthermore, we show the effectiveness of carfilzomib according to line of therapy, reasons for stopping treatment, and toxicity from

treatment. This study was approved by the Danish Data Protection Agency (18/22825) and the Danish Patient Safety Authority (3-3013-2047/2).

Methods.

We conducted a nationwide retrospective analysis of RRMM patients treated with daratumumab (N=635) identified from local electronic health records or department registries. Among those, 251 patients had received treatment with carfilzomib. Supplementary Figure 1 presents patient selection. Study cut-off for inclusion of patients was 1. January 2019. In this cohort, patients either failed carfilzomib and thereafter received daratumumab or vice versa within 3 years. Data were collected by audit of electronic health records. The lines of therapy and drug combinations were annotated according to IMW consensus (16). Reasons for termination of treatment were collected, and toxicity was specified further. Due to the retrospective nature of the data collection response to treatment was assessed as very good partial remission (VGPR) or better, partial response (PR), and less than partial response (<PR) according to IMW criteria (17). Overall response rate (ORR) was PR or better. Time to next treatment (TNT) was used as outcome parameter instead of progression free survival (PFS) because initiation dates of new treatment were annotated with high accuracy in the health records and in drug registries. TNT was defined as the time from the date of initiation of a line of treatment (LOT) until either the date of initiation of the subsequent LOT, the date of death, or the date of last follow-up in patients still on the last LOT. The database was linked to the Danish Multiple Myeloma Registry (DMMR) for characteristics at diagnosis (18, 19). Cytogenetic abnormalities (CA) by FISH with a cut-off of 10% were available in more than 75% of the patients. High-risk CA was t(4;14), t(14;16), and/or del17p. Data on amp1q status were available in 75% of the patients.

Statistical analysis

Categorical variables were presented with numbers and percentages and compared between groups by Chi-square tests or Fisher's exact test in the case of small numbers. Continuous variables were presented with median and interquartile range (IQR). Continuous variables were compared between multiple groups by Kruskal-Wallis test and between two groups by Mann-Whitney test. Time to next treatment was presented by Kaplan-Meier curves. Median times and proportions at specific times were extracted from the Kaplan-Meier statistics and presented with 95% confidence intervals (CI). Differences between groups were calculated by log-rank tests. Furthermore, a Cox proportional hazard model was calculated and hazard ratios (HR) with 95% confidence intervals were presented. To find risk factors correlated to TNT, a univariate and a multivariable Cox proportional hazard model were applied. Only significant variables from the univariate models were entered in the multivariable model. Time to follow up was calculated with the reverse Kaplan-Meier method. All p-values were two-sided and p-values ≤0.05 were considered statistically significant. R version 3.6.1 was used for all calculations.

Results

Patient characteristics and subgroups

A total of 251 RRMM patients were treated with carfilzomib (Table 1). Of these patients 150 were treated with carfilzomib before daratumumab and 101 were treated with carfilzomib after daratumumab. No patients received treatment with carfilzomib in combination with daratumumab when daratumumab was given for the first time. The medium age at diagnosis of the 251 patients was 62 years (IQR 55-69 years), the median age at start of carfilzomib treatment 68 years (IQR 60-73 years) and the median follow-up 64.1 months (IQR 30.8–82.7 months). The

median number of LOTs given before carfilzomib was 3 (IQR 2-5). Sixteen of the 150 patients treated with carfilzomib before daratumumab (10.7%) were still on daratumumab treatment at data cut-off. Most patients were treated with carfilzomib in combination with dexamethasone alone (43.0%); otherwise with IMiDs (22.3%), cyclophosphamide (21.5%) or other regimens (9.6%) (Supplementary Table 1). Supplementary figure 2 shows the number of patients treated with carfilzomib and daratumumab according to LOT. The characteristics of the patients treated with carfilzomib before and after daratumumab and patients not treated with carfilzomib are shown in Table 1. The group of patients treated with carfilzomib differed from patients not treated with carfilzomib in the following parameters: They were younger, more were treated up-front with HDM-ASCT, more had relapse within 18 months from HDM-ASCT, and more had high-risk CA and amp1q. There was no significant difference between the groups according to time from diagnosis to start of carfilzomib treatment, gender, PS, ISS, M-protein, elevated LDH, or creatinine at diagnosis, and FISH results. In the cohort of patients treated with carfilzomib after daratumumab, more patients had high-risk CA by t(4;14), t(14;16), and del17p (43.3% versus 30.3%), more patients had amp1q (41.0% versus 30.1%), and more had a relapse within 18 months from HDT (47.4% versus 34.4%). Patients treated with carfilzomib before daratumumab were less likely to have received prior treatment with lenalidomide and/or pomalidomide than patients that received daratumumab before carfilzomib (58.7% vs. 95% and 24.7% vs. 49.5%, respectively). Nearly all patients had received prior bortezomib (98.7% vs. 98.0%).

Outcome of treatment with carfilzomib

Figure 1 shows the TNT for carfilzomib according to carfilzomib-containing regimens given as 2nd, 3rd, 4th, 5th and 6th line of therapy, respectively.

Median TNT for carfilzomib was 12 months when used in 2nd line. This was superior to TNT for carfilzomib when administrated in 3rd LOT or later with no difference in TNT irrespectively of LOT. ORR and VGPR are presented in Table 1. A higher percentage of patients treated with carfilzomib before daratumumab had ≥VGPR compared to patients treated with carfilzomib after daratumumab (31.7% versus 17.4%; p=0.018). Figure 2 shows the TNT for carfilzomib when given before and after daratumumab. Both median TNT and duration of treatment were short when carfilzomib was given before (7.1; CI:5.4-9.0 months, 4.6; CI:3.8-5.6 months, respectively) and after daratumumab (4.3; CI:3.4-6.0 months; 3.7; CI: 2.8-4.2 months, respectively)(Table 1), and no significant difference was found between the two patient cohorts. Likewise, TNT for daratumumab when given before (5.6; CI:3.9-7.4 months) and after carfilzomib (4.9; CI:3.7-6.2 months) was short.

Carfilzomib given as 2nd Line of therapy

Outcome of carfilzomib was superior when given in 2nd LOT (Figure 1). We characterized the patients treated with carfilzomib in 2nd LOT (Supplementary Table 2). Thirty-nine patients received carfilzomib as part of their 2nd LOT and 17 (46%) of these received carfilzomib as part of induction treatment before salvage HDM-ASCT. Patients in the HDM-ASCT group may have participated in the CARFI trial (NCT02572492) that investigated carfilzomib-cyclophosphamide-dexamethasone (KCd) induction before HDT and randomization to either observation or carfilzomib-dexamethasone maintenance treatment. More patients treated with salvage HDM-ASCT had been treated with up-front HDM-ASCT and were thus likely to be fitter than patients in the non-HDM-ASCT group. Furthermore, the TNT from first to second LOT was longer in the salvage HDM-ASCT

group indicating a less aggressive disease. This corresponds to the better outcome of carfilzomib used in second LOT.

Reasons for stopping carfilzomib and toxicity of carfilzomib

The reasons for discontinuation of carfilzomib containing treatment are shown in Supplementary Table 3. Most patients discontinued treatment because of progressive disease (48%), insufficient response (8%), or as part of the treatment plan (6%). However, 14% of all patients stopped carfilzomib treatment due to toxicity. The toxicity of carfilzomib when given before and after daratumumab is shown in Supplementary Table 4. More patients treated with carfilzomib before daratumumab stopped treatment due to toxicity. The most common toxicities that led to discontinuation of treatment were infection (4%) and dyspnoea (3%).

Discussion

In this study we selected patients treated with carfilzomib before daratumumab and vice versa within a short time frame, and therefore we cannot compare the outcome of patients in our study to those of the RCT´s ASPIRE and ENDEAVOR (20, 21).

We find that most patients stopped treatment due to progression/insufficient response and toxicity. TNT was longest when carfilzomib was used in second LOT as part of induction treatment before salvage transplant with HDM-ASCT. Otherwise, TNT was poor irrespectively of timing of carfilzomib. The poor TNT in our cohort correspond to other real-life studies on treatment with carfilzomib where the median TNT/PFS has been found to be 3.2 to 9.4 months (22-25). A recent real-world study by Rocchi et al. found a median PFS of 19.8 months in patients treated with carfilzomib-lenalidomide-dexamethasone with a median of 2 prior LOTs. In our cohort the patients

were older, only one fifth were treated with carfilzomib in combination with IMiDs, more patients had high-risk disease and half of the patients received carfilzomib in 4th LOT or later.

An equal part of patients terminated treatment with carfilzomib due to toxicity (mostly infection and dyspnoea) as observed in the ASPIRE and ENDEAVOR studies (20, 26). Only 3% in our cohort of patients discontinued treatment due to cardiotoxicity which is less than findings from the SEER database (27). In addition, only 1% discontinued treatment with carfilzomib due to renal failure and is less than observed by Mian et al. and Fotiu et al. (27-29). A likely explanation for these differences is that our patients on average were younger, fitter and duration of treatment with carfilzomib was shorter.

The retrospective design of this study is an unavoidable limitation that only allows us to generate hypotheses of causation. Data of carfilzomib treatment was collected nationwide and there was no limitation in access to treatment. However, there may still be variations in treatment strategy depending on patients' wishes and preference of the treating physician. The well described cardiotoxicity to carfilzomib is expected to influence the choice of treatment. Patients treated with carfilzomib were younger and more had been exposed to up-front HDM-ASCT than patients not treated with carfilzomib. This implies that the treating physician selected patients for treatment with carfilzomib that were fitter and our results support the findings by Chari et al (30). Furthermore, our results confirm that the treating physician may be more likely to choose treatment with carfilzomib in patients with more aggressive or active disease (30). Adherence to treatment is important for a good outcome and some patients may have higher quality of life when not attending the hospital weekly for treatment.

Several studies have shown that patients perish between subsequent lines of therapy. (31, 32) Making the right choice of treatment for a patient at a given time may therefore be crucial. Our results indicate that in this cohort of patients, outcome of carfilzomib is poor irrespectively of timing and that outcome of daratumumab is equally poor in patients with an early relapse after carfilzomib. This finding adds knowledge to the general understanding that patients with high-risk CA and an early relapse after HDM-ASCT need attention and should be considered for new promising treatment strategies.

Legends to Figures.

Figure 1: Time to next treatment (TNT) for patients treated with carfilzomib according to the line of treatment (LOT) in which carfilzomib was administered. Median TNT for carfilzomib as part of 2^{nd} LOT (red) was 12.3 months. TNT for 2^{nd} LOT was longer than median TNT for all other LOTs (4-6 months) ($p<0.0001$). There was no significant difference in median TNT for 3^{rd}, 4^{th}, 5^{th}, or 6^{th} and more LOTs.

Figure 2: Time to next treatment (TNT) of carfilzomib given for the first time according to treatment before (blue) versus after (red) treatment with daratumumab. Median TNT for treatment with carfilzomib before versus after daratumumab was 7.1 and 4.3 months, respectively. A trend towards longer TNT of carfilzomib administered before versus after daratumumab was found ($p=0.06$).

Table 1. Baseline demographics and clinical characteristics

	Carfilzomib before daratumumab	Carfilzomib after daratumumab	Patients not treated with carfilzomib	P value
N	150	101	384	
Diagnose <2008: N (%)	17 (11.3)	20 (19.8)	40 (10.4)	
Diagnose 2009-2019: N (%)	133 (88.7)	81 (80.2)	344 (89.4)	
Age, median at diagnosis (IQR)	61 (56-69)	64 (55-70)	68 (60-73)	<0.0001
Age at start of carfilzomib treatment, median (IQR)	66 (60-73)	69 (61-75)		0.20
Gender: male %	58.7	64.4	52.3	0.054
PS at diagnosis				
PS 0-2: N (%)	130 (95.6)	84 (95.5)	329 (94.3)	0.80
PS 3-4: N (%)	6 (4.4)	4 (4.5)	20 (5.7)	
Missing N	14	13	35	
Follow-up after carfilzomib: mo	NR	20.9	NR	
ISS stage at diagnosis				
I:N (%)	43 (34.1)	23 (28.4)	95 (29.3)	0.860
II: N (%)	38 (30.2)	31 (38,3)	135 (41.7)	
III: N (%)	45(35.7)	27 (33.3)	94 (29.7)	
Missing N	24	20	60	
Serum M-protein at diagnosis				
IgG M-protein: N (%)	78 (56.5)	51 (58.0)	208 (59.6)	0.810
IgA M protein: N (%)	36 (26.1)	21 (23.9)	74 (21.2)	
Light chain: N (%)	20 (14.5)	15 (17.0)	54 (15.5)	
Other: N (%)	4 (2.9)	1 (1.1)	13 (3.7)	
Missing: N	12	13	35	
Serum LDH above normal at diagnosis: N (%)[†]	37 (27.2)	35 (37.6)	91 (25.9)	0.080
Missing: N	14	8	33	
Creatinine > 177umol/L at diagnosis: N (%)	29 (22.6)	15 (16.0)	46 (12.7)	0.084
Missing N	9	7	22	
Prior treatment				
HDM-ASCT in first line	93 (62.0)	57 (56.4)	159 (41.4)	<0.0001
Relapse < 18 mo from HDM- ASCT, N (%)	32 (34.4)	27 (47.4)	46 (28.9)	0.041
Bortezomib prior to carfilzomib: N (%)	148 (98.7)	99 (98.0)	NR	
Lenalidomide prior to carfilzomib: N (%)	88 (58.7)	96 (95.0)	NR	<0.0001
Pomalidomide prior to carfilzomib: N (%)	37 (24.7)	50 (49.5)	NR	<0.0001
FISH analysis available N (%)	113 (75.3)	83 (87.1)	272 (70.8)	0.061
High-risk CA at diagnosis del17p, t(14;16), t(4;14) N (%)	33 (30.3)	36 (43.3)	66 (24.4)	0.004
Amp1q at diagnosis N (%)	34 (30.1)	34 (41.0)	70 (25.8)	0.028
Response to carfilzomib- containing regimen				
OOR N (%)	101 (67.3)	47 (46.5)		0.014
≥VGPR: N (%)	46 (31.7)	16 (17.4%)	NR	0.018
Missing N	5	9		
Lines of therapy given before first time carfilzomib				
1. N (%)	39 (26)	0	NR	

2. N (%)	35 (23)	16 (16)	NR	
3. N (%)	21 (14)	23 (23)	NR	
4 or more N (%)	55 (37)	62 (61)	NR	
TNT from first carfilzomib treatment: median mo (CI)	7.1 (5.4-9.0)	4.3 (3.4-6.0)	NR	0.06
Duration of treatment with carfilzomib: median mo (CI)	4.6 (3.8-5.6)	3.7 (2.8-4.2)	NR	1.0
Time from diagnosis to start of carfilzomib: median mo (IQR)	39.8 (24.1-65.0)	41.3 (22.5-89.2)	NR	0.51
TNT for daratumumab before carfilzomib mo (CI)		5.6 (3.9-7.4)	20.3 (17.6-30.4)	
TNT for daratumumab after carfilzomib [‡] mo (CI)	4.9 (3.7-6.2)			

[†] LDH levels: Age>70 years, upper limit is ≥255 UL, age ≤70, upper limit is ≥205 UL

NR = not relevant; N= number; PS= performance status; CI = confidence interval; mo= months, IQR = inter quantile range, , CA: cytogenetic abnormalities

[‡]No of patients still on daratumumab after carfilzomib was 25.

References

1. Klausen TW, Gregersen H, Abildgaard N, Andersen NF, Frølund UC, Gimsing P, et al. The majority of newly diagnosed myeloma patients do not fulfill the inclusion criteria in clinical phase III trials. Leukemia. 2019;33(2):546-9.
2. Shah JJ, Abonour R, Gasparetto C, Hardin JW, Toomey K, Narang M, et al. Analysis of Common Eligibility Criteria of Randomized Controlled Trials in Newly Diagnosed Multiple Myeloma Patients and Extrapolating Outcomes. Clinical lymphoma, myeloma & leukemia. 2017;17(9):575-83.e2.
3. Costa LJ, Hari PN, Kumar SK. Differences between unselected patients and participants in multiple myeloma clinical trials in US: a threat to external validity. Leukemia & lymphoma. 2016;57(12):2827-32.
4. Redder L, Klausen TW, Vangsted AJ, Gregersen H, Andersen NF, Pedersen RS, et al. Validation of the UK myeloma research alliance risk profile, a new clinical prediction model for outcome in patients with newly diagnosed multiple myeloma not eligible for autologous stem cell transplantation; a population-based study from the Danish national multiple myeloma registry. British journal of haematology. 2021;193(1):119-24.
5. Cook G, Royle KL, Pawlyn C, Hockaday A, Shah V, Kaiser MF, et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. The Lancet Haematology. 2019;6(3):e154-e66.
6. Gregersen H, Vangsted AJ, Abildgaard N, Andersen NF, Pedersen RS, Frolund UC, et al. The impact of comorbidity on mortality in multiple myeloma: a Danish nationwide population-based study. Cancer medicine. 2017;6(7):1807-16.
7. Kumar S, Mahmood ST, Lacy MQ, Dispenzieri A, Hayman SR, Buadi FK, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone marrow transplantation. 2008;42(6):413-20.
8. Vangsted AJ, Klausen TW, Andersen NF, Abildgaard N, Gang AO, Gregersen H, et al. Improved survival of multiple myeloma patients with late relapse after high-dose treatment and stem cell support, a population-based study of 348 patients in Denmark in 1994-2004. European journal of haematology. 2010;85(3):209-16.
9. Venner CP, Connors JM, Sutherland HJ, Shepherd JD, Hamata L, Mourad YA, et al. Novel agents improve survival of transplant patients with multiple myeloma including those with high-risk disease defined by early relapse (<12 months). Leukemia & lymphoma. 2011;52(1):34-41.
10. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Early relapse after single auto-SCT for multiple myeloma is a major predictor of survival in the era of novel agents. Bone marrow transplantation. 2015;50(2):204-8.
11. Majithia N, Rajkumar SV, Lacy MQ, Buadi FK, Dispenzieri A, Gertz MA, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia. 2016;30(11):2208-13.
12. Ong SY, de Mel S, Chen YX, Ooi MG, Surendran S, Lin A, et al. Early relapse post autologous transplant is a stronger predictor of survival compared with pretreatment patient

factors in the novel agent era: analysis of the Singapore Multiple Myeloma Working Group. Bone marrow transplantation. 2016;51(7):933-7.
13. Helm-Petersen S, Sorrig R, Klausen TW, Preiss B, Frolund UC, Helleberg C, et al. Early relapsed disease of multiple myeloma following up-front HDM-ASCT: a study based on the Danish Multiple Myeloma Registry in the period 2005 to 2014. Leukemia. 2018.
14. Moreau P, Cavo M, Sonneveld P, Rosinol L, Attal M, Pezzi A, et al. Combination of international scoring system 3, high lactate dehydrogenase, and t(4;14) and/or del(17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(20):2173-80.
15. Thidemann Andersen K, Klausen T, Abildgaard N, Klarskov Andersen M, Frost Andersen N, Christian Frolund U, et al. Causes of early death in multiple myeloma patients treated with high-dose therapy followed by autologous stem cell transplantation: A study based on the nationwide Danish Multiple Myeloma Registry. American journal of hematology. 2017;92(10):E611-e4.
16. Rajkumar SV, Richardson P, San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood. 2015;126(7):921-2.
17. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-5.
18. Gimsing P, Holmstrom MO, Klausen TW, Andersen NF, Gregersen H, Pedersen RS, et al. The Danish National Multiple Myeloma Registry. Clinical epidemiology. 2016;8:583-7.
19. Holmstrom MO, Gimsing P, Abildgaard N, Andersen NF, Helleberg C, Clausen NA, et al. Causes of early death in multiple myeloma patients who are ineligible for high-dose therapy with hematopoietic stem cell support: A study based on the nationwide Danish Myeloma Database. American journal of hematology. 2015;90(4):E73-4.
20. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng WJ, Oriol A, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(10):1327-37.
21. Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018;36(8):728-34.
22. Danhof S, Schreder M, Rasche L, Strifler S, Einsele H, Knop S. 'Real-life' experience of preapproval carfilzomib-based therapy in myeloma - analysis of cardiac toxicity and predisposing factors. European journal of haematology. 2016;97(1):25-32.
23. Durie B CG, Goldschmidt H et al. . The use of carfilzomib and bortezomib in routine clinical practice: results from preamble, an ongoing, observational cohort study in multiple myeloma. Haematologica. 2017;102(s2):520. Abstract E1269.
24. Cerchione C FK, Peluso I et al. Carfilzomib-lenalidomide-dexamethasone in the manegement of relapsed and refractory multible myeloma: a real-life experience. Haematologica. 2017;217;102(S2):804.
25. Hobbs M PJ, Fonder A, et al. Efficacy of carfilzomib (K), pomalidomide (P), and dexamethasone (d) in heavily pretreated patients with relapsed/refractory multiple myeloma (RRMM) in a real world setting. Blood cancer journal. 2016;128:3337.

26. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. The New England journal of medicine. 2015;372(2):142-52.
27. Bishnoi R, Xie Z, Shah C, Bian J, Murthy HS, Wingard JR, et al. Real-world experience of carfilzomib-associated cardiovascular adverse events: SEER-Medicare data set analysis. Cancer medicine. 2021;10(1):70-8.
28. Fotiou D, Roussou M, Gakiopoulou C, Psimenou E, Gavriatopoulou M, Migkou M, et al. Carfilzomib-associated renal toxicity is common and unpredictable: a comprehensive analysis of 114 multiple myeloma patients. Blood cancer journal. 2020;10(11):109.
29. Mian HS, Fiala MA, Sanchez L, Vij R, Wildes TM. Renal failure among multiple myeloma patients utilizing carfilzomib and associated factors in the "real world". Annals of hematology. 2021;100(5):1261-6.
30. Chari A, Richardson PG, Romanus D, Dimopoulos MA, Sonneveld P, Terpos E, et al. Real-world outcomes and factors impacting treatment choice in relapsed and/or refractory multiple myeloma (RRMM): a comparison of VRd, KRd, and IRd. Expert review of hematology. 2020;13(4):421-33.
31. Yong K, Delforge M, Driessen C, Fink L, Flinois A, Gonzalez-McQuire S, et al. Multiple myeloma: patient outcomes in real-world practice. British journal of haematology. 2016;175(2):252-64.
32. Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clinic proceedings. 2004;79(7):867-74.