Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Real-World Outcome in the pre-CAR-T Era of Myeloma Patients Qualifying for CAR-T Cell Therapy

Simon Brechbühl[1], Ulrike Bacher[2], Barbara Jeker[1] and Thomas Pabst[1].

[1] Department of Medical Oncology, Inselspital, University Hospital Bern; University of Bern; Bern, Switzerland.
[2] Department of Hematology and Central Hematology Laboratory, Inselspital, University Hospital Bern; University of Bern; Bern, Switzerland.

Competing interests: The authors declare no conflict of Interest.

Abstract. *Background:* CAR-T cell therapy is likely to be introduced starting from 2021 in patients with relapsed/refractory myeloma (r/r MM) in Europe. In order to qualify for commercial CAR-T treatment, it is assumed that r/r MM patients will have to be exposed to at least three lines of previous treatments including lenalidomide, bortezomib and anti-CD38 treatment. However, the outcome of this particular subgroup of r/r MM patients is largely unknown whereas this knowledge is crucial to estimate the possible benefit of eventual CAR-T treatment.
Methods: In this non-interventional, retrospective single-center study, we analyzed all subsequent r/r MM patients treated between 01/2016 (when anti-CD38 treatment was commercially introduced in Switzerland) and 04/2020 at the University Hospital of Bern. Patients were eligible for the study if they had received at least three lines of treatment including one proteasome inhibitor (PI), one immunomodulatory drug (IMID) and one anti-CD38 antibody, and if they were in need of subsequent treatment and effectively received further lines of treatment.
Results: Among 56 patients fulfilling the criteria of at least three lines of treatment including PI, IMID and anti-CD38 treatment, only 34 (60%) effectively received subsequent further therapy. This suggests that 40% of r/r MM patients never receive additional treatment after at least three lines of treatment including PI, IMID and anti-CD38 treatment. For patients receiving further treatment, the median number of previous lines of treatment was 4.5 (range 2-12), including autologous stem cell transplantation in 31 (91%) patients. 13 (37%) patients were penta-refractory. The most frequently used treatment options were IMID/dexamethasone treatment in 11 (32%) patients, followed by PI/dexamethasone in 10 (29%) patients. 21 (62%) patients received two or more additional lines of therapy. The median PFS was 6.6 months (range 0–36.6 months), the median TTNT was 7.5 months (range 1.4-24.5 months) and the median OS was 13.5 months, (range 0.1-38 months) for the first subsequent treatment. The overall response rate (ORR) to the first subsequent treatment was 41%, with a median duration of the response of 5 months (range 1-37 months). 12% of the patients achieved VGPR or better, with a median duration of response of 8 months (range 3-37 months).
Conclusions: Myeloma patients refractory after at least three lines of anti-CD38/PI/IMID treatment have a poor prognosis with a PFS of 6.6 months and OS of 13.5 months. These data may serve as reference to compare the potential benefit of CAR-T treatment in this group of myeloma patients when available in the near future.

Correspondence to: Thomas Pabst M.D.; Associate Professor; Department of Medical Oncology; Inselspital; University Hospital; 3010 Bern; Switzerland. Tel.: +41 31 632 8430; Fax: +41 31 632 3410. E-mail: thomas.pabst@insel.ch.

Introduction. Due to demographic changes, the incidence of multiple myeloma (MM) is increasing, and 2% of all cancer-related mortalities are caused by MM.[1,2] The introduction of novel therapeutic compounds including proteasome inhibitors (PI, e.g. bortezomib, carfilzomib, and ixazomib), immunomodulatory drugs (IMiD, thalidomide, lenalidomide, and pomalidomide) and monoclonal antibodies (e.g. daratumumab and isatuximab, targeting CD38) have prolonged survival of patients with MM. Therefore, prevalence of multiple myeloma has been significantly increasing.[3-8] However, almost all myeloma patients will ultimately relapse at some stage, and the disease remains incurable.[7-11] This emphasizes the unmet need for new and more effective therapeutic modalities. Inhibition of exportin1 by selinexor,[12,13,14] protease inhibition by nelfinavir,[15,16] and anti-SLAMF7 activity by elotuzumab[17] represent recent approaches.

Since 2019, therapy with genetically modified T-cells expressing a chimeric antibody receptor (CAR-T) was commercially introduced for the treatment of relapsed/refractory (r/r) aggressive B-cell lymphomas and acute lymphoblastic B-cell leukemia in Switzerland. Currently, CAR-T cell therapy is further evaluated for patients with r/r MM in clinical studies and will soon be in commercial use.[3,6,9,18-33] The majority of the clinical CAR-T cell trials in multiple myeloma target the B-cell maturation antigen (BCMA), which shows predominant expression on myeloma and normal plasma cells, in contrast to low or absent expression on other cell compartments.[6,34-36]

As CAR-T therapy will soon be introduced for commercial treatment of r/r MM patients, it is of utmost interest to learn the possible benefit of this novel therapeutic option for this subset of myeloma patients. As a basis, knowledge of the outcome of such r/r MM patients in the pre-CAR-T era is crucial. In the present study, we, therefore, aimed at characterizing this group of r/r MM patients as a basis for later comparisons with CAR-T treated MM patients. CAR-T in MM will most likely be restricted to patients with at least three previous lines of treatment with at least one PI, one IMID and one anti-CD38 antibody. Consequently, this study intends to describe the outcome of MM patients effectively receiving further treatment for progressive disease after three lines of treatment including at least one PI, one IMID and one anti-CD38 antibody.

Methods.
Patients. This non-interventional, single-center, retrospective study analyzed patients with r/r MM diagnosed between 01/2016 (when anti-CD38 treatment was commercially introduced in Switzerland) and 04/2020 at the University Hospital of Bern, Switzerland. Patients were eligible for the study, if they had received at least one proteasome inhibitor, one immunomodulatory drug and an anti-CD38 antibody, as well as a total of at least three lines of treatment. The study was approved by a decision of the local ethics committee of Bern, Switzerland, and all participants have given written informed consent.

Treatment. We summarized lenalidomide, thalidomide and pomalidomide as immunomodulatory drugs (IMiD's). The group of proteasome inhibitors (PI) comprised carfilzomib, bortezomib and ixazomib. Alkylating agents (Alky) were melphalan, bendamustine, cyclophosphamide, vincristine, doxurubicin and etoposide. Antibody treatment comprised anti-CD38-antibodies (daratumumab; isatuximab) and anti-SlamF7 antibody (elotuzumab).

Definitions. Progression-free survival (PFS) was calculated from the start of the first treatment after inclusion in the study until first progression of MM or death of any cause, whichever occurred first. Progression was defined as an increase of at least 25% in measurable monoclonal immunoglobulin in serum or urine or an increase of ≥25% in urinary light chains.[37,38] Overall response rate (ORR) was defined as the percentage of patients with at least partial response or better according to IMWG Uniform Response Criteria.[10] Time to next treatment (TTNT) was the time between start of the first treatment after inclusion in the study until the first day of the next treatment regimen. Overall survival (OS) was assessed from the start of the first treatment after inclusion in the study until death or last follow-up with a data cut-off at April 04, 2020, whichever occurred first.

Statistical analysis. PFS, TTNT, and OS were calculated according to the Kaplan-Meier method and were depicted using Graphpad (Graphpad, Prism 8, Version 8.2.1 (441), August 20, 2019). Statistical analyses were double-sided, and p-values below .05 were considered significant.

Results.
Patients. We identified 56 multiple myeloma (MM) patients, who had received at least one PI, one IMID and one anti-CD38 treatment, and a total of at least three lines of treatment, between 01/2016 and 04/2020 at the University Hospital Bern, Switzerland. Of these 56 patients, 34 effectively received subsequent further

Table 1. Patient characteristics at first diagnosis of the multiple myeloma.

Parameter	Results
Age at diagnosis, median (range)	63 (42-78)
<65 years, n (%)	20 (59%)
≥65 years, n (%)	14 (41%)
<75 years, n (%)	33 (97%)
≥75 years, n (%)	1 (3%)
Sex	
males/females (ratio)	25/9 (2.8)
Paraprotein subtype, n (%)	
IgG	16 (57%)
IgA	12 (43%)
kappa light chain	20 (63%)
lambda light chain	12 (38%)
light chain only, n (%)	5 (15%)
BM infiltration, median (range (%)	0,6 (20%-99%)
Hypercalcemia (>2.6 mmoL/L), n (%)	7 (21%)
Renal failure, n (%)	11 (32%)
Serum creatinine median, μmol/L (range)	85 (49-492)
Anemia (<100 g/L), n (%)	25 (74%)
Hemoglobin, median g/L (range)	101 (71-146)
Osteolytic lesion, n (%)	23 (68%)
ß2-microglobulin >3.5mg/L n (%)	19 (56%)
Albumin < 3.5 g/dL, n (%)	22 (65%)
LDH, >480 U/L	4 (12%)
Stage R-ISS	
I, n (%)	10 (29%)
II, n (%)	6 (18%)
III, n (%)	18 (53%)
Cytogenetics	
Available, n (%)	21 (62%)
At least 1 high-risk aberration, n (% of known)	6 (29%)

IgG/IgA/IgM: Immunoglobulin type G, A, M; BM: bone marrow; LDH: Lactate dehydrogenase; R-ISS: Revised International Staging System; High risk aberration: t(4;14), t(14;16), t(14;20), del(17/17p), gain(1q), del(13).

Table 2. Treatments prior and including first daratumumab treatment.

Parameter	Results	
Lines of prior therapy including daratumumab		
2-3, n (%)	15	(44%)
4-5, n (%)	5	(15%)
6-7, n (%)	9	(26%)
8-9, n (%)	3	(9%)
>9, n (%)	2	(6%)
Prior therapy including daratumumab, n (%)		
PI mono	19	(56%)
PI+Alky	26	(76%)
PI+IMiD	10	(29%)
IMiD mono	19	(56%)
IMiD+Alky	4	(12%)
Alky mono	4	(12%)
Anti-CD38 antibody mono	16	(47%)
Anti-CD38 antibody+PI	7	(21%)
Anti-CD38 antibody+IMiD	11	(32%)
Anti-SLAMF7 antibody+IMiD	1	(3%)
Anti-SLAMF7 antibody+PI+IMiD	1	(3%)
HDCT/ASCT	31	(91%)
Maintenance post HDCT/ASCT	21	(62%)

#: Numbers of; PI mono: Proteasome inhibitor; PI + Alky: Proteasome inhibitor and alkylating agent; PI + IMiD: Proteasome inhibitor and immunomodulatory drug; IMiD mono: Immunomodulatory drug; IMiD + Alky: Immunomodulatory drug and alkylating agent; Alky mono: Alkylating agent; Anti-CD38 antibody mono: Daratumumab; Anti-CD38 antibody + PI: Daratumumab and proteasome inhibitor; Anti-CD38 antibody + IMiD: Daratumumab and immunomodulatory drug; Anti-CD38 antibody + IMiD + Alky: Daratumumab and immunomodulatory drug and alkylating agent; Anti-SLAMF7 antibody mono: Elotuzumab (Anti-SLAMF7 antibody); Anti-SLAMF7 antibody + PI + IMiD: Elotuzumab and proteasome inhibitor and immunomodulatory drug; Dexa mono: Dexamethasone; HDCT/ASCT: High-dose chemotherapy and autologous stem cell transplantation.

treatment, and these 34 patients were representing the cohort (100%) analyzed in this study. The patient characteristics at first diagnosis of these MM patients are summarized in **Table 1**. The median age at diagnosis was 62 years (range 35-78). A total of 27 (66%) patients had R-ISS disease stage of II or III; and 8 (24%) patients had at least one high-risk aberration including the gain of 1q, deletion 17p, or translocation t(4;14), t(6;14), or t(14;20).

Prior therapies including daratumumab. Among the 34 patients fulfilling the criteria of three treatment lines, including PI, IMID, and anti-CD38 treatment, and effectively receiving subsequent therapy line(s), the median number of previous lines was 4.5 (range 2-12 lines). 24 (55%) patients had four or more prior therapy lines, mainly because anti-CD38 treatment was first given late in these patients. HDCT and ASCT were performed in 31 (91%) patients. The prior treatment lines are summarized in **Table 2**. 14 (40%) patients were quad-refractory, thus refractory to bortezomib, lenalidomide, carfilzomib, and pomalidomide, and 13 (37%) patients were penta-refractory, thus refractory also to daratumumab.

First treatment line after inclusion. The median interval from the initial diagnosis to the first treatment after fulfilling the study criteria was 67 months (range 19 to 189 months). 11 (32%) patients received one subsequent treatment line, 13 (38%) patients received two subsequent treatment lines, and 8 (24%) patients

Table 3. Treatments after first daratumumab treatment.

Parameter	Results	
Therapy after daratumumab, n (%)		
PI mono	10	(29%)
PI+Alky	2	(6%)
PI+IMiD	6	(18%)
IMiD mono	11	(32%)
IMiD+Alky	5	(15%)
Alky mono	9	(26%)
Anti-CD38 antibody mono	5	(15%)
Anti-CD38 antibody+PI	6	(18%)
Anti-CD38 antibody+IMiD	3	(9%)
Anti-CD38 antibody+IMiD+Alky	1	(3%)
Anti-SLAMF7 antibody mono	1	(3%)
Anti-SLAMF7 antibody+IMiD	5	(15%)
HDCT/ASCT, n (%)	6	(18%)
Maintenance therapy after HDCT/ASCT	2	(6%)
#Pat, still on daratumumab at cutoff, n (%)	2	(6%)
#Pat, died before cutoff date, n (%)	18	(53%)
No of lines after daratumumab, n (%)		
1 line	11	(32%)
2 lines	13	(38%)
3 lines	5	(15%)
4 lines	1	(3%)
5 lines	2	(6%)
Overall response rate, %	41%	
95% Confidence interval	±3	
VGPR (VGPR&CR), %	12%	
95% Confidence interval	±9	
Median duration of response, months (range)	6	(1.7-37)
Time from initial diagnosis until first treatment after Daratumumab, median months (range)	67	(19-189)
Follow up time, median months (range)	12	(0.2-38)

#: Numbers of; PI mono: Proteasome inhibitor; PI + Alky: Proteasome inhibitor and alkylating agent; PI + IMiD: Proteasome inhibitor and immunomodulatory drug; IMiD mono: Immunomodulatory drug; IMiD + Alky: Immunomodulatory drug and alkylating agent; Alky mono: Alkylating agent; Anti-CD38 antibody mono: Daratumumab (Anti-CD38 antibody); Anti-CD38 antibody + PI: Daratumumab and proteasome inhibitor; Anti-CD38 antibody + IMiD: Daratumumab and immunomodulatory drug; Anti-CD38 antibody + IMiD + Alky: Daratumumab and immunomodulatory drug and alkylating agent; Anti-SLAMF7 antibody mono: Elotuzumab (Anti-SLAMF7 antibody); Anti-SLAMF7 antibody + IMiD: Elotuzumab and immunomodulatory drug; HDCT/ASCT: High Dose chemotherapy and autologous stem cell transplantation; Cutoff date: 04. February 2020; Overall response rate: Patient with partial, very good partial, and complete response to the first medication after first daratumumab treatment; VGPR: Very good partial response to the first medication after first daratumumab treatment; CR: Complete response to the first medication after first daratumumab treatment.

received three or more lines of treatment (**Table 3**). The most frequent treatment line was IMID/dexamethasone in 11 (32%) patients, followed by PI/dexamethasone in 10 (29%) patients, alkylating agents in 9 (26%) patients, daratumumab combined with a PI in 6 (18%) patients, and PI combined with IMID in 6 (18%) patients. Six (18%) patients received HDCT/ASCT during relapse treatment.

The ORR to the first treatment after study inclusion was 41%, with a median duration of response of 5 months (range 1 to 37 months). 12% of the patients had an excellent partial response or better, with a median duration of this response of 8 months (range 3 to 37 months). So far, 33 (59%) patients have died, all due to disease progression.

Outcome. The median PFS after the first treatment line after inclusion in the study was 6.6 months (range, 0 to 36.6 months; **Figure 1A**). For the patients with two or more further treatment lines, the median PFS was 6.6 months (range, 0 to 24.5 months) compared to median PFS of 5 months (range, 0.1 to 36.6 months) for those with only one further line. The median TTNT between the first and the second treatment line was 7.5 months (range 1.4-24.6 months) for the patients with effectively at least two further lines of treatment (**Figure 1B**). The median OS of the cohort was 13.5 months (range, 0.1 to 38.0 months) after starting the first line of treatment within the study (**Figure 1C**). For patients with two or more further treatment lines, the OS was 15.6 months (range, 3.5 to 38) compared to 7.5 months (range, 0.1 to 36.6 months) for the patients with only one further treatment line.

Discussion. This study describes the clinical characteristics, treatment lines, and clinical outcomes of a heavily pretreated group of myeloma patients in Switzerland. The inclusion criteria were selected in order to mirror the criteria likely to be used candidates for subsequent CAR-T treatment in the near future. In particular, we included r/r MM patients who had previous therapy with at least three treatment lines, including PI, IMID, and anti-CD38 therapy.[39-41]

The patients in our CAR-T candidate cohort had a median of five prior therapy lines, similar to pretreated myeloma patient cohorts described in the literature that had received a median of two to seven previous therapies.[3,9,12,40,42-45] In particular, 40% of our patients were quad-refractory, and 37% were penta-refractory. These proportions were comparable to previous studies on similar patient cohorts.[12,13]

Patients received a median of two further therapy lines. Following the start of the first treatment line in our study, we found a short median PFS of 6.6 months, highlighting the short duration of response in the advanced disease stages of r/r MM patients. Related studies on retreatment with IMiD's and PI's after anti-CD38 treatment reported even shorter survival rates, with a median PFS of 4 months for patients receiving PI's, and three months for IMID's.[46] In similar patient cohorts, the median PFS was 3.7 months for selinexor and 3.4 months for nelfinavir.[12,16]

In contrast, CAR-T studies describe a median PFS between 7.7,[3] 7.9[47] and 11.8[9] months in patients with r/r MM. Therefore, there is a difference of 3 to 5 months of the median PFS compared to our findings in this heavily
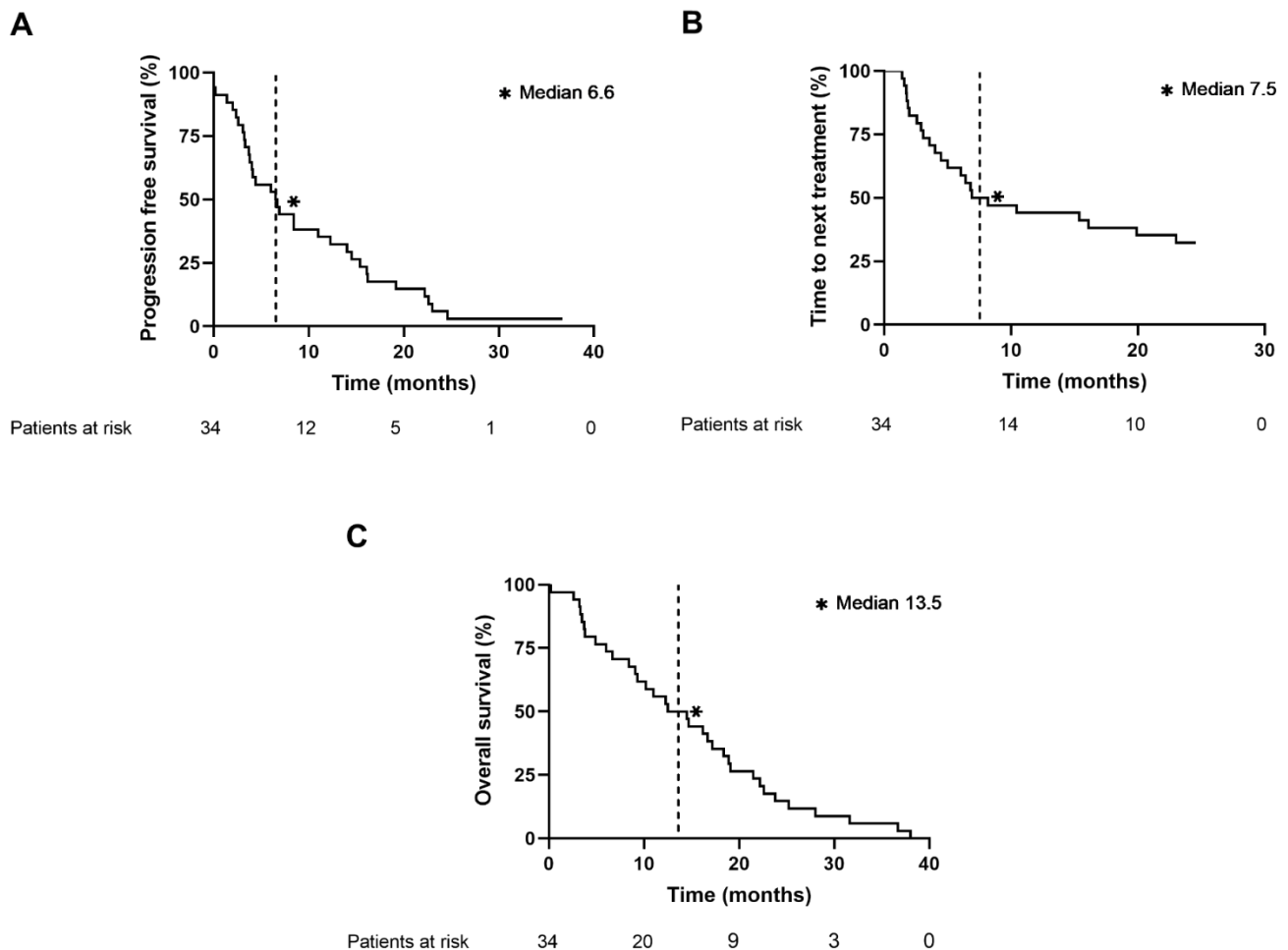
Figure 1. Kaplan-Meyer curves depicting (**A**) progression free survival, (**B**) time to next treatment and (**C**) overall survival of myeloma patients for the first subsequent treatment line after inclusion in the study, thus, after at least three previous treatment lines.

pretreated myeloma patient group. This difference emphasizes the anti-myeloma efficacy of CAR-T cell treatment compared to conventional therapies in r/r MM patients.

Overall survival (OS) rates were reported between 1.7 and 5.5 months in anti-CD38 refractory patients.[45,48] Selinexor and nelfinavir studies found OS rates of 9.3[13] and 21.6 months,[16] respectively. This suggests that the OS rate of 13.5 months in our cohort compares rather favorably to other series. The heavier pretreated patient group might explain the difference in the selinexor studies and the less heavily pretreated patient group in the nelfinavir studies, respectively, as well as in the higher proportion of quad- and penta- refractory patients in the post daratumumab studies by Pick et al. and Lakshmann et al. [45,48]

We identified a median TTNT of 7.5 months in our cohort. Lakshman et al reported a median TTNT of 5.7 months in patients refractory to daratumumab and combination therapies similar to our results.[48] In contrast, Driessen et al. described better TTNT (10 and 12 months) in two patients treated with nelvinavir.[15]

The overall response rate was 41% in this study; in others, the ORR was 21%[13] and 25%[12] in the selinexor studies, 33%[15] and 55%[16] in the nelfinavir studies 28.6%, 52%, and 67% in three studies investigating retreatment after daratumumab.[45,46] In contrast, the ORR was higher with 60%,[47] 81%,[3] and 85%[9] in three CAR-T cell studies.

Similarly, the response duration was 4 months for nelfinavir,[16] 4.4 months[12] and 5 months[13] for selinexor. In contrast, CAR-T studies reported response duration between 7.9 and 13 months,[47] with a dose-dependent duration of the responses, with a median duration of response of 10.9 months.[9]

In our study, the median follow-up from the start of the first treatment was 12 months, comparable to previous myeloma studies, which reported median follow-ups between 5.5 and 36 months.[9,16,45,47,48] The median interval from initial diagnosis until the first treatment in the study was 67 months (range 19 to 189 months). This seems comparable to other reports with intervals between 45.6 and 79.2 months for similar

patient groups.[9,12,13,45,48]

Conclusions. This study describes an instead poorly reported group of MM patients, which had received at least three lines of treatment and must have had PI, IMID, and anti-CD38 treatment. In addition, the patients must have had further progression, and at least one line of subsequent treatment must have been given. This first line of subsequent treatment is most likely the situation in which CAR-T treatment will become available. Our study identified for this line of treatment with currently available, non-CAR-T treatment options a median PFS of 6.6 months, a median TTNT of 7.5 months, and the median OS was 13.5 months. These numbers may serve as a reference when benefits of CAR-T treatment in r/r MM will be discussed, or those of bispecific CD269 antibodies.[50-53]

References:

1. Bundesamt für Statistik. Schweizerischer Krebsbericht 2015 Multiples Myelom. Neuchâtel; 2017. Available from: https://www.bfs.admin.ch/bfs/de/home/statistiken/kataloge-datenbanken/publikationen.assetdetail.2281157.html

2. Krebsliga Schweiz. Multiples Myelom - Plasmazellmyelom - Eine Information der Krebsliga. Bern, Krebsliga Schweiz 2018. Available from: https://www.krebsliga.ch/ueber-krebs/krebsarten/multiples-myelom-plasmazellmyelom/

3. Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. JCO 2018;36(22):2267-80. https://doi.org/10.1200/JCO.2018.77.8084 PMid:29812997 PMCid:PMC6067798

4. Palumbo A, Anderson K. Multiple Myeloma. N Engl J Med 2011;364(11):1046-60. https://doi.org/10.1056/NEJMra1011442 PMid:21410373

5. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the international myeloma working group. Leukemia 2016;30(5):1005-17. https://doi.org/10.1038/leu.2015.356 PMid:26710887

6. Mikkilineni L, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for multiple myeloma. Blood 2017;130(24): 2594-02. https://doi.org/10.1182/blood-2017-06-793869 PMid:28928126 PMCid:PMC5731088

7. Sonneveld P. Management of multiple myeloma in the relapsed/refractory patient. Hematology 2017;2017(1):508-17. https://doi.org/10.1182/asheducation-2017.1.508 PMid:29222299 PMCid:PMC6142583

8. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia 2012;26(1):149-57. https://doi.org/10.1038/leu.2011.196 PMid:21799510 PMCid:PMC4109061

9. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med 2019;380(18):1726-37. https://doi.org/10.1056/NEJMoa1817226 PMid:31042825

10. Kumar S. Treatment of newly diagnosed multiple myeloma in transplant-eligible patients. Current Hematologic Malignancy Reports 2011;6(2):104-12. https://doi.org/10.1007/s11899-011-0083-0 PMid:21394431

11. Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: an update. Drugs 2018;78(1):19-37. https://doi.org/10.1007/s40265-017-0841-y PMid:29188449 PMCid:PMC5756574

12. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med 2019;381(8):727-38. https://doi.org/10.1056/NEJMoa1903455 PMid:31433920

13. Vogl DT, Dingli D, Cornell RF, et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. JCO 2018;36(9):859-66. https://doi.org/10.1200/JCO.2017.75.5207 PMid:29381435 PMCid:PMC6905485

14. Chen C, Siegel D, Gutierrez M, et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. Blood 2018;131(8):855-63. https://doi.org/10.1182/blood-2017-08-797886 PMid:29203585

15. Driessen C, Kraus M, Joerger M, et al. treatment with the HIV protease inhibitor nelfinavir triggers the unfolded protein response and may overcome proteasome inhibitor resistance of multiple myeloma in combination with bortezomib: a phase I trial (SAKK 65/08). Haematologica 2016;101(3):346-55. https://doi.org/10.3324/haematol.2015.135780 PMid:26659919 PMCid:PMC4815726

16. Hitz F, Kraus M, et al. Nelfinavir and lenalidomide/dexamethasone in patients with lenalidomide-refractory multiple myeloma. a phase I/II trial (SAKK 39/10). Blood Cancer J 2019;9(9):70. https://doi.org/10.1038/s41408-019-0228-2 PMid:31455773 PMCid:PMC6711992

17. Bazarbachi AH, Al Hamed R, Malard F, Harousseau J-L, Mohty M. Relapsed refractory multiple myeloma: a comprehensive overview. Leukemia 2019;33(10):2343-57. https://doi.org/10.1038/s41375-019-0561-2 PMid:31455853

18. Turtle CJ, Hanafi L-A, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. Journal of Clinical Investigation 2016;126(6):2123-38. https://doi.org/10.1172/JCI85309 PMid:27111235 PMCid:PMC4887159

19. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371(16):1507-17. https://doi.org/10.1056/NEJMoa1407222 PMid:25317870 PMCid:PMC4267531

20. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. The Lancet 2015;385(9967):517-28. https://doi.org/10.1016/S0140-6736(14)61403-3

21. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Science Translational Medicine 2014;6(224):224-25. https://doi.org/10.1126/scitranslmed.3008226 PMid:24553386 PMCid:PMC4684949

22. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Science Translational Medicine 2013;5(177ra38):1-9.

23. Turtle CJ, Hanafi L-A, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8 + and CD4 + CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med 2016;8(355ra116):1-12. https://doi.org/10.1126/scitranslmed.aaf8621 PMid:27605551 PMCid:PMC5045301

24. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell

malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. JCO 2015;33(6):540-9.
https://doi.org/10.1200/JCO.2014.56.2025
PMid:25154820 PMCid:PMC4322257

25. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. Molecular Therapy 2017;25(10):2245-53.
https://doi.org/10.1016/j.ymthe.2017.07.004
PMid:28803861 PMCid:PMC5628864

26. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. JCO 2017;35(16):1803-13.
https://doi.org/10.1200/JCO.2016.71.3024
PMid:28291388 PMCid:PMC5455597

27. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood 2010;116(20):4099-102.
https://doi.org/10.1182/blood-2010-04-281931
PMid:20668228 PMCid:PMC2993617

28. Makita S, Yoshimura K, Tobinai K. Clinical development of anti-CD19 chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma. Cancer Sci 2017;108(6):1109-18.
https://doi.org/10.1111/cas.13239
PMid:28301076 PMCid:PMC5480083

29. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 2018;378(5):449-59.
https://doi.org/10.1056/NEJMoa1709919
PMid:29385376 PMCid:PMC6637939

30. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377(26):2531-44.
https://doi.org/10.1056/NEJMoa1707447
PMid:29226797 PMCid:PMC5882485

31. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378(5):439-48.
https://doi.org/10.1056/NEJMoa1709866
PMid:29385370 PMCid:PMC5996391

32. Jain MD, Bachmeier CA, Phuoc VH, Chavez JC. Axicabtagene ciloleucel (KTE-C19), an anti-CD19 CAR T therapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin's lymphoma. Ther Clin Risk Manag 2018;14:1007-17.
https://doi.org/10.2147/TCRM.S145039
PMid:29910620 PMCid:PMC5987753

33. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Molecular Therapy 2017;25(1):285-95.
https://doi.org/10.1016/j.ymthe.2016.10.020
PMid:28129122 PMCid:PMC5363293

34. Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clinical Cancer Research 2013;19(8):2048-60.
https://doi.org/10.1158/1078-0432.CCR-12-2422
PMid:23344265 PMCid:PMC3630268

35. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood 2016;128(13):1688-700.
https://doi.org/10.1182/blood-2016-04-711903
PMid:27412889 PMCid:PMC5043125

36. Novak AJ, Darce JR, Arendt BK, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood 2004;103(2):689-94.
https://doi.org/10.1182/blood-2003-06-2043
PMid:14512299

37. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation: annotation. British Journal of Haematology 1998;102(5):1115-23.
https://doi.org/10.1046/j.1365-2141.1998.00930.x
PMid:9753033

38. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from international myeloma working group. JCO 2015;33(26):2863-9.
https://doi.org/10.1200/JCO.2015.61.2267
PMid:26240224 PMCid:PMC4846284

39. Samaras P, Bargetzi M, Betticher DC, et al. Updated recommendations for diagnosis and treatment of plasma cell myeloma in Switzerland [Internet] Swiss Med Wkly. 2019 [cited 2020 Apr 16]; Available from:
https://doi.emh.ch/smw.2019.20031
https://doi.org/10.4414/smw.2019.20031
PMid:30943308

40. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. Mayo Clinic Proceedings 2016;91(1):101-19.
https://doi.org/10.1016/j.mayocp.2015.11.007
PMid:26763514 PMCid:PMC5223450

41. Kumar SK, Callander NS, Hillengass J, et al. NCCN guidelines insights: multiple myeloma, version 1.2020. Journal of the National Comprehensive Cancer Network 2019;17(10):1154-65.
https://doi.org/10.6004/jnccn.2019.0049
PMid:31590151

42. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375(8):754-66.
https://doi.org/10.1056/NEJMoa1606038
PMid:27557302

43. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood 2017;130(8):974-81.
https://doi.org/10.1182/blood-2017-05-785246
PMid:28637662 PMCid:PMC5570682

44. Tzogani K, Penninga E, Schougaard Christiansen ML, et al. EMA review of daratumumab for the treatment of adult patients with multiple myeloma. The Oncologist 2018;23(5):594-602.
https://doi.org/10.1634/theoncologist.2017-0328
PMid:29371479 PMCid:PMC5947446

45. Pick M, Vainstein V, Goldschmidt N, et al. Daratumumab resistance is frequent in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis. Eur J Haematol 2018;100(5):494-501.
https://doi.org/10.1111/ejh.13046
PMid:29453884

46. Oostvogels R, Jak M, Raymakers R, Mous R, Minnema MC. Efficacy of retreatment with immunomodulatory drugs and proteasome inhibitors following daratumumab monotherapy in relapsed and refractory multiple myeloma patients. Br J Haematol 2018;183(1):60-7.
https://doi.org/10.1111/bjh.15504
PMid:30080247 PMCid:PMC6220946

47. Trudel S, Lendvai N, Popat R, et al. Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. The Lancet Oncology 2018;19(12):1641-53.
https://doi.org/10.1016/S1470-2045(18)30576-X

48. Lakshman A, Abeykoon JP, Kumar SK, et al. Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials. Am J Hematol 2017;92(11):1146-55.
https://doi.org/10.1002/ajh.24883
PMid:28799231

49. Swissmedic. DARZALEX [Internet]. Compendium.ch. [cited 2020 April 21]; Available from:
https://compendium.ch/product/1337302-darzalex-inf-konz-100-mg-5ml/MPro#MPro7100

50. Seckinger A, Delgado JA, Moser S, et al. Target expression, generation, preclinical activity, and pharmacokinetics of the BCMA-T cell bispecific antibody EM801 for multiple myeloma treatment. Cancer Cell 2017;31(3):396-410.
https://doi.org/10.1016/j.ccell.2017.02.002
PMid:28262554

51. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia 2020;34(4):985-1005.
https://doi.org/10.1038/s41375-020-0734-z
PMid:32055000 PMCid:PMC7214244

52. Cohen AD. Myeloma: next generation immunotherapy. Hematology 2019;2019(1):266-72.
https://doi.org/10.1182/hematology.2019000068
PMid:31808859 PMCid:PMC6913481

53. Pillarisetti K, Edavettal S, Mendonça M, et al. A T-cell-redirecting bispecific G-protein-coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma. Blood 2020;135(15):1232-43.
https://doi.org/10.1182/blood.2019003342
PMid:32040549 PMCid:PMC7146017