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

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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.

Keywords: Myeloma; Real-world assessment; Candidates for CAR-T cell therapy; Pre-study; Survival.

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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 neflinavir,\(^15\)\(^-\)\(^16\) 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, doxorubicin 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 regime. 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%)                 |
| β2-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%)                 |
| Cytogeneatics                    |                          |
| 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).

Results: 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 received three treatment lines.

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; Dexamethasone; HDCT/ASCT: High-dose chemotherapy and autologous stem cell transplantation.
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, alkylation 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.3,9,12,16,40-45 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 7.947 and 11.8 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

### 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.
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.\textsuperscript{45,48} Selinexor and nelfinavir studies found OS rates of 9.3\textsuperscript{13} and 21.6 months,\textsuperscript{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.\textsuperscript{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.\textsuperscript{48} In contrast, Driessen et al. described better TTNT (10 and 12 months) in two patients treated with nelfinavir.\textsuperscript{15}

The overall response rate was 41\% in this study; in others, the ORR was 21\%\textsuperscript{13} and 25\%\textsuperscript{12} in the selinexor studies, 33\%\textsuperscript{15} and 55\%\textsuperscript{16} in the nelfinavir studies 28.6\%, 52\%, and 67\% in three studies investigating retreatment after daratumumab.\textsuperscript{45,46} In contrast, the ORR was higher with 60\%,\textsuperscript{47} 81\%,\textsuperscript{3} and 85\%\textsuperscript{9} in three CAR-T cell studies. Similarly, the response duration was 4 months for nelfinavir,\textsuperscript{16} 4.4 months\textsuperscript{12} and 5 months\textsuperscript{13} for selinexor. In contrast, CAR-T studies reported response duration between 7.9 and 13 months,\textsuperscript{47} with a dose-dependent duration of the responses, with a median duration of response of 10.9 months.\textsuperscript{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.\textsuperscript{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

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**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.

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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 PL, 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

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