Cost Effectiveness and Resource Allocation

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Third-line multiple myeloma treatment of inpatients in a German cancer center: analysis of potential cost savings due to decreased renal insufficiency

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Abstract

Background Renal insufficiency is one of the most common complications in the treatment of multiple myeloma (MM). The administration of isatuximab showed improved patient outcome regarding the occurrence of renal insufficiency. Building on the results of the ICARIA-MM study, the aim of this study was to quantify the potential cost savings due to a prevented progress of renal insufficiency.

Methods Real-life accounting data of the University Hospital Cologne (Germany) of inpatients with MM between 2016 and 2020 were analyzed regarding the presence of renal insufficiency. The health-economic impact of a less severe renal insufficiency due to improved renal filtration on German Diagnosis-Related Groups (G-DRG) tariffs was modelled.

Results The analysis revealed a total of 74 hospital cases with MM. The vast majority ($n=64$; 86.5%) were allocated to the G-DRG code R61, summarizing patients with "lymphoma and non-acute leukemia". Based on a reduction of stage 3 renal failure to stage 2, the model showed cost saving potential in patients with acute renal failure ranging from € 3,101 to € 4,642 per case.

Conclusion The analysis quantifies for the first time the economic saving potential of improved renal function in patients with relapsed/refractory multiple myeloma in the German healthcare system through the administration of isatuximab.

Keywords Multiple myeloma, Renal insufficiency, Cost savings, Isatuximab, Hospital management

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Introduction

Around 6,350 people are diagnosed with multiple myeloma (MM) in Germany per year. This makes MM the third most common hematological disease after leukemia and non-Hodgkin lymphoma [1]. The causes for the development of MM are mostly unexplored. Exposure to pesticides and rubber-processing products at work, obesity, and presence of other diseases are examples of currently discussed risk factors [2]. In the German healthcare system, which is segregated into inpatient and outpatient care, the latter incorporates most commonly MM treatment. Exceptions are autologous stem cell transplantation in first-line therapies or the treatment of complications and adverse events of MM. Renal insufficiency (RI) and acute renal failure are common complications of multiple myeloma [3]. Several studies identified impaired renal function as an unfavorable prognostic factor regarding treatment success and mortality [4, 5]. For the treatment of MM, numerous and constantly expanding combinations of drugs are available for respective lines of therapy [6].

The anti-CD38 monoclonal antibody *isatuximab* is indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. *Isatuximab* is further indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy [7].

The ICARIA-MM (NCT02990338) study showed a hazard ratio of 0.599 for progression free survival (PFS) for patients receiving *isatuximab*/*pomalidomide/dexamethasone* compared to patients treated with *pomalidomide/dexamethasone* alone (Isa-Pd vs. Pd) [8]. The improvement in PFS represented a 40.1% reduction in the risk of disease progression or death in patients treated with Isa-Pd [8]. In a subgroup analysis of the ICARIA-MM trial the median PFS for patients with RI was 9.5 months with Isa-Pd ($n = 55$) and 3.7 months with Pd ($n = 49$) accordingly [9]. In contrast to chronic kidney disease, the subgroup with acute kidney failure showed no short-term improvement in renal filtration performance in the analysis of the ICARIA-MM [9].

Given the medical benefit of third-line isatuximab treatment in patients with relapsed refractory MM ((r/r) MM) and RI similar to the subgroup analysis of the ICARIA-MM trial, this study aimed to descriptively analyse the reimbursement of patients from a hospital management perspective. In addition, the impact of less severe renal insufficiency on the reimbursement was modeled since isatuximab may improve the renal filtration in patients with (r/r) MM.

Materials and methods

To quantify hospital treatment costs of patients similar to the ICARIA-MM trial, reimbursement data of the cancer center in the Department I of Internal Medicine of the University Hospital Cologne (UHC) between Jan-01-2016 and Apr-30-2020 were retrospectively analyzed. Patients were identified by operation and procedure codes (OPS) and International Statistical Classification of Diseases and Related Health Problems codes, Version 10, German Modification (ICD-10-GM). Eligibility criteria were MM not having achieved complete remission (C90.00) as main diagnosis together with secondary diagnosis RI (N17 or N18). The clinical documentation system of the UHC (Orbis, AGFA) was searched for eligible patients. Patients with insufficient billing information, undergoing apheresis (OPS code: 5-410), autologous stem cell transplantation (OPS codes: 5-411 or 8-805), or other reference to first or second-line therapy were excluded. From a technical point of view, billing information do not provide any information on the delineation of the therapy line if administrable in several therapy lines. Immunomodulating agents that, according to their approval, can be also administered in first- and second-line therapy were also excluded. Thus, patients treated with combinations of proteasome inhibitor *carfilzomib* (OPS code: 6-008.9*), *bortezomib* (OPS code: 6-001.9*), monoclonal antibodies *daratumumab* (OPS code: 6–009.a*), *elotuzumab* (OPS code: 6–009.d) or immunomodulatory *lenalidomid* (OPS code: 6 – 003.g*) were not considered. Remaining patients were descriptively analyzed per year using median values and ranges of the following measures: Number of patients and cases, age, gender, admission diagnosis, German Diagnosis Related Groups (G-DRG) tariffs, length of stay, treatment on intensive care unit (ICU), ventilation hours, and case mix.

Subgroups were built distinguished by secondary diagnosis according to the level of RI: acute renal failure ((ICD-10-GM code: N17) or chronic kidney disease ((ICD-10-GM code: N18).

A subgroup analysis for the most common combinations of G-DRG tariffs and RI secondary diagnosis group was performed. By successively modelling a reduced RI stadium, the economic effect of improved renal filtration performance was quantified. Differences in reimbursement due to changed G-DRG tariffs were calculated without changing other case-relevant parameters. Regardless of the inclusion period, the G-DRG tariff catalog and the grouping logic from 2022 were applied. All monetary values were given in Euro (EUR) and discounting was not performed. A base-rate of 3,833.07 EUR was assumed [10].

Results

In total, 720 cases (398 patients) with MM not having achieved complete remission (C90.00) were identified at initial review of the medical-chart data. Fifteen cases were excluded due to insufficient accounting data and 538 cases were excluded because no secondary diagnosis was coded for RI. Further patients were excluded due to previous treatments such as apheresis ($n = 9$), stem cell transplantation ($n = 38$) or administration of at least one of the following immunomodalating agents: *Carfilzomib* ($n = 13$), *daratumumab* ($n = 28$), *lenalidomid* ($n = 19$), *elotuzumab* ($n = 0$), or *bortezomib* ($n = 0$). As some patients received multiple of the aforementioned agents, a total of 46 patients were excluded due to treatment with an immunomodulating agent. Therefore, the analysis included data of 74 cases representing 63 individual patients (Fig. 1). All patients were admitted with diagnosis MM not having achieved complete remission (C90.00).

As summarized in Table 1, some of the 63 patients were treated several times. With a median age of 64.5 years (range: 40–84 years) over the entire period, the median age varied between 58 years in 2020 and 66.5 years in 2018. Across all years, most patients were male. Except for 2018, the proportion of men was between 60.0% and 66.7%.

Table 2 shows median values of reimbursement-relevant key figures. The median length of stay was 13 days

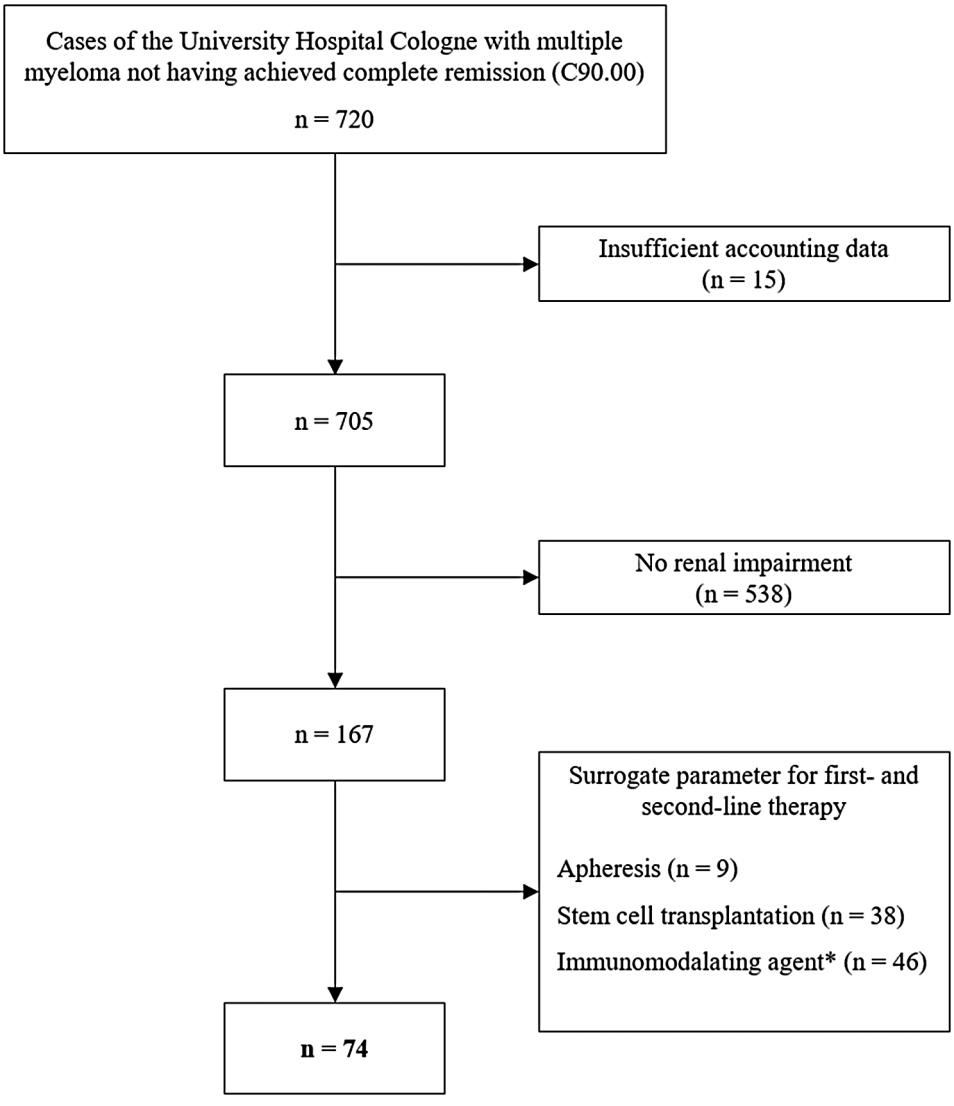

Fig. 1 Flow chart and exclusion criteria

Table 1 Patient characteristics

	2016	2017	2018	2019	2020†	Total
No. of patients	16	14	14	17	3	63
No. of cases	18	15	20	18	3	74
Age (range)	58.5 (48–79)	63 (43–78)	66.5 (54–84)	66 (40–75)	58 (43–80)	64.5 (40–84)
Sex						
Female (%)	7 (38.9%)	6 (40.0%)	1 (5.0%)	7 (38.9%)	1 (33.3%)	22 (29.7%)
Male (%)	11 (61.1%)	9 (60.0%)	19 (95.0%)	11 (61.1%)	2 (66.7%)	52 (70.3%)

† 01. January – 30. April

Table 2 Reimbursement relevant key figures (median values)

	2016	2017	2018	2019	2020†	Total
Length of stay (range)						
across all G-DRGs	16 (2–56)	15 (3–92)	12.5 (1–34)	11.5 (2–76)	12 (5–18)	13 (1–92)
ICU treatment (%)						
across all G-DRGs	7 (38.9%)	8 (53.3%)	7 (35.0%)	11 (61.1%)	1 (33.3%)	34 (46.0%)
Invasive ventilation (%)						
across all G-DRGs	1 (5.6%)	3 (20.0%)	2 (10.0%)	4 (22.2%)	0 (0.0%)	10 (13.5%)
Case-mix index (range)						
across all G-DRGs	2.95 (0.76–6.73)	2.02 (0.78–29.87)	1.92 (0.33–12.57)	1.44 (0.33–25.16)	0.9 (0.68–3.60)	1.99 (0.33–29.87)
Secondary diagnosis with reference to renal insufficiency						
Acute renal failure (N17.-)	8	8	10	12	2	40
Chronic kidney disease (N18.-)	10	6	10	7	1	34
Cases per G-DRG (%)						
across all G-DRGs	18 (100.0%)	15 (100.0%)	20 (100.0%)	18 (100.0%)	3 (100.0%)	74 (100.0%)
A09B	-	1 (6.7%)	-	1 (5.6%)	-	2 (2.7%)
A36A	-	-	-	2 (11.1%)	-	2 (2.7%)
R01A	-	1 (6.7%)	-	-	-	1 (1.4%)
R36Z	-	2 (13.3%)	1 (5.0%)	-	-	3 (4.1%)
R61A	6 (33.3%)	1 (6.7%)	2 (10.0%)	1 (5.6%)	1 (33.3%)	11 (14.9%)
R61B	3 (16.7%)	-	1 (5.0%)	1 (5.6%)	-	5 (6.8%)
R61D	3 (16.7%)	3 (20.0%)	8 (40.0%)	4 (22.2%)	-	18 (24.3%)
R61E	1 (5.6%)	2 (13.3%)	-	-	-	3 (4.1%)
R61F	-	-	-	1 (5.6%)	-	1 (1.4%)
R61G	-	-	3 (15.0%)	2 (11.1%	1 (33.3%)	6 (8.1%)
R61H	5 (27.8%)	5 (33.3%)	4 (20.0%)	5 (27.8%)	1 (33.3%)	20 (27.0%)
R65B	-	-	1 (5.0%)	1 (5.6%)	-	2 (2.7%)

G-DRG: German Diagnosis Related Groups

ICU: intensive care unit

† 01. January – 30. April

(range: 1–92 days) with a decreasing trend over the observational period. Overall, 46.0% of all cases ($n = 34$) have been transferred to the ICU and 13.5% ($n = 10$) were mechanically ventilated on ICU. The median case-mix index was 1.99 (range: 0.33–29.87 points) with a decreasing trend over the years. Six different G-DRG tariffs were identified. Identified in 20 cases (27.0%), the most frequent G-DRG tariff was R61H 'Lymphoma and non-acute leukemia without certain complicating factors' followed by G-DRG tariff R61D `Lymphoma and non-acute leukemia' with 18 cases (24.3%). Seven different levels of resource consumption of the G-DRG tariff R61 "lymphoma and non-acute leukemia" were identified.

As displayed in Table 3, the secondary diagnosis with reference to RI were distributed as follows: 40 cases were coded with a secondary diagnosis of the group 'acute renal failure' (ICD-10-GM code: N17) while the remaining 34 cases were associated with a 'chronic kidney disease' (ICD-10-GM code: N18). Stage 3 was most common in both groups of kidney disease. In another

Table 3 Subgroup analysis based on secondary diagnosis with reference to renal insufficiency

OPS code	2016	2017	2018	2019	2020†	Total
Acute renal failure (N17.-)	8	8	10	12	2	40
N17.03	0	0	1	0	0	1
N17.22	0	0	1	0	0	1
N17.83	0	0	1	0	0	1
N17.91	2	3	3	4	1	13
N17.92	1	0	2	3	0	6
N17.93	5	5	2	5	1	18
Chronic kidney disease (N18.-)	10	6	10	7	1	34
N18.1	0	0	1	0	0	1
N18.2	1	0	1	1	0	3
N18.3	6	2	7	2	0	17
N18.4	1	1	1	0	1	4
N18.5	2	2	0	3	0	7
N18.9	0	1	0	1	0	2

OPS: operation and procedure codes

† Jan-01 – Apr-30

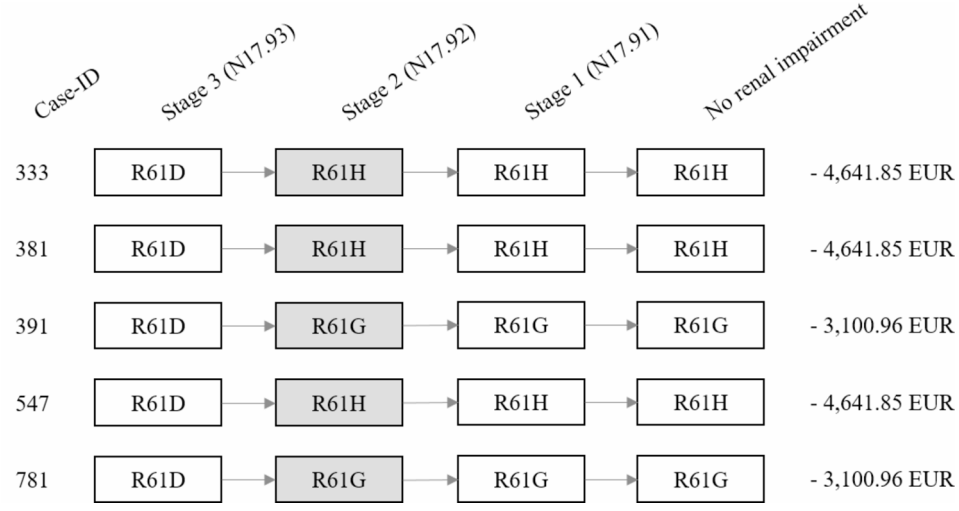

Fig. 2 Change of the G-DRG tariff due to an improved stage of renal insufficiency

two cases, the degree of severity was not specified ((ICD-10-GM code: N18.9).

The subgroup analysis of R61 cases showed an effect on the G-DRG tariff in terms of resource consumption in five out of 38 cases. Based on the lower disease severity of acute RI in the model, a shift from G-DRG tariff R61D to a lower-rated one was detected in all cases. The coding of unspecified acute renal failure stage 2 without histological findings instead of the originally coded stage 3 led to a change in the G-DRG tariff in five cases (Fig. 2). The model identified a total saving potential of 20,128 EUR (range: 3,101 EUR – 4,642 EUR) in the examined cohort.

Discussion

In the last decades, the treatment of MM developed dynamically regarding both, new therapy options and therapy-associated costs [11–13]. Leading German oncological associations recommend the introduction of the CD38 antibody *isatuximab* as a part of a triple therapy in their joint guideline [14] This is largely due to the medical benefits such as delayed progression, improved disease control, achieving longer remission and having manageable side effects.

The improved renal function due to the administration of *isatuximab* has already been demonstrated in a subgroup analysis of the ICARIA-MM trial [9] Patients receiving isatuximab in combination with Pd (Isa-Pd) had an improved PFS compared to the administration of Pd alone and showed complete renal response rates of 71.9% and 38.1%, respectively. Renal response rates lasting longer than 60 days were also in favor of Isa-Pd (38,1%) compared to Pd (19.0%).

The clinical picture of chronic and acute renal insufficiency, however, is to be distinguished. According to the

KDIGO ("Kidney Disease: Improving Global Outcomes") guidelines, acute renal failure is present when at least one of the three following criteria is met: (1) an increase in serum creatinine of at least 0.3 mg/dl within 48 h above a measured baseline value, (2) an increase in serum creatinine compared to a measured baseline or the patient's predicted baseline by at least 50% within the previous 7 days, or (3) a decrease in urinary output to less than 0.5 mL/kg/h for at least 6 h [15] The ICD-10-GM staging of acute kidney failure is based on the KDIGO guideline [16].

Taking the results of the ICARIA-MM trial as starting point, the underlying analysis showed that a reduced RI may lead to economic benefits. The effect was shown due to a modelled improvement from stage 3 to unspecified acute renal failure stage 2 without histological findings. Including 74 hospital cases, modelled cost savings ranged from 3,101 EUR to 4,642 EUR per case. As the German reimbursement system is based on flat rates, a change regarding the secondary diagnosis did not necessarily affect the G-DRG tariff. However, secondary diagnoses can affect the patient clinical complexity level (PCCL), which in turn can lead to a more or less resource-intensive G-DRG. In the analysis at hand, the reduction of PCCL did not influence the G-DRG tariff if other resource-consuming services such as agranulocytosis or chemotherapy were provided.

From a health economic perspective, the administration of *isatuximab* becomes economically feasible when list prices of several therapy components are massively discounted (>60%) [17]. According to Lauer-Taxe®, a manufacturer price reduction for isatuximab was already implemented on Nov-01-2022, Jan-01-2022 and Jul-01-2023.

Although the analysis was conducted in all conscience, this analysis has some limitations. Using real-life accounting data carries the risk of faulty or incomplete data documentation. It was intended to define a patient cohort similar to the ICARIA-MM trial, difficulties arose, however, in the differentiation of second and third-line treatment solely based on medical coding. Therefore, surrogate parameters for first- and second-line treatments, such as the administration of stem cells, were used as exclusion criteria. Services reimbursed outside of the G-DRG tariffs (e.g. additional fees) were not considered but may contain further saving potential if becoming obsolete due to a reduction in RI.

The underlying analysis focused exclusively on changes in the renal function; a holistic view of the MM treatment pathway may reveal correlating side effects. The introduction of a specific OPS code for the parenteral administration of *isatuximab* in 2023 allows a systematic and comprehensive monitoring of (r/r) MM treatment with *isatuximab* in following investigation as it enables precise case selection and analysis (e.g. calculation of G-DRG tariffs) without surrogate parameters. The consideration of the acquisition costs of isatuximab and outpatient treatment costs along the entire patient pathway would make it possible to examine the health economic effects from the perspective of the payers. Including data sets of several cancer centers would further improve validity.

Acknowledgements
Not applicable.

Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Florian Jakobs and Paymon Ahmadi. The first draft of the manuscript was written by Florian Jakobs and Paymon Ahmadi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding
This work was funded by Sanofi. The funding body had no role in the design of the study, the collection/analysis/interpretation of data and the writing of the manuscript.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Due to the retrospective study design and a pseudonymised documentation of underlying cost data, no ethical vote was needed.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 29 August 2023 / Accepted: 30 November 2024
Published online: 05 March 2025

References

1. Erdmann F, Spix C, Katalinic A et al. *Krebs in Deutschland für 2017/2018.* 2021.
2. Sergentanis TN, Zagouri F, Tsilimidos G, et al. Risk factors for multiple myeloma: a systematic review of Meta-analyses. Clin Lymphoma Myeloma Leuk. 2015;15(10):563–e577561.
3. Bladé J, Rosiñol L. Renal, hematologic and infectious complications in multiple myeloma. Best Pract Res Clin Haematol. 2005;18(4):635–52.
4. Yadav P, Cook M, Cockwell P. Current trends of renal impairment in multiple myeloma. Kidney Dis (Basel). 2016;1(4):241–57.
5. Dimopoulos MA, Cheung MC, Roussel M, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica. 2016;101(3):363–70.
6. Rajkumar SV. Treatment of multiple myeloma. Nat Reviews Clin Oncol. 2011;8(8):479–91.
7. European Medicines Agency. Summary of Product Characteristics [Sarclisa]. https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf. Accessed January 10, 2023.
8. Richardson PG, Perrot A, San-Miguel J, et al. Isatuximab plus Pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. Lancet. 2022;23(3):416–27.

9. Dimopoulos MA, Leleu X, Moreau P, et al. Effect of isatuximab plus pomalidomide/dexamethasone on renal impairment in relapsed/refractory multiple myeloma: ICARIA-MM study subgroup analysis. Leukemia. 2021;35:562–72.
10. Vereinbarung gemäß § 10 Absatz 9 KHEntgG für den Vereinbarungszeitraum. 2022. 2022; https://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/krankenhaeuser/budgetverhandlungen/bundesbasisfallwert/KH_BBFW_2022.pdf. Accessed August 21, 2022.
11. Rajkumar SV. Value and cost of Myeloma Therapy. Am Soc Clin Oncol Educ Book. 2018;38:662–6.
12. Gulla A, Anderson KC. Multiple myeloma: the (r)evolution of current therapy and a glance into future. Haematologica. 2020;105(10):2358–67.
13. Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia. 2017;31(9):1915–21.
14. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF). Accessed Februar 06, : Diagnostik, Therapie und Nach-sorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom, Langversion 1.0, 2022, AWMF-Registernummer: 018/035OL, https://www.leitlinienprogrammonkologie.de/leitlinien/multiples-myelom/. (2023).
15. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Supplements. 2012;2(1):1–138.
16. Bundesinstitut für Arzneimittel und Medizinprodukte. ICD-10-GM Version. 2022: Kapitel XIV Krankheiten des Urogenitalsystems (N00-N99) - Niereninsuffizienz (N17-N19) 2022; https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2022/block-n17-n19.htm. Accessed August 19, 2022.
17. Canadian Agency for Drugs & Technologies in Health (CADTH). CADTH Reimbursement Recommendation - Isatuximab (Sarclisa). 2021; August 21. https://canjhealthtechnol.ca/index.php/cjht/article/view/pc0256/522. Accessed 2022.

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