Wiesława Adamiec
CARITA FOUNDATION

ACCESS TO MODERN MEDICAL THERAPIES FOR MULTIPLE MYELOMA

Poland vs Europe

Report listing medications available in Poland and comparing them with European standards to allow an objective review of their availability for therapeutic purposes.

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Introduction

Wiesława Adamiec's Carita Foundation has been supporting patients with multiple myeloma for more than 10 years. Over that period of time, therapeutic capabilities have changed and the awareness of patients has been growing thanks to our wide-scale education activities. Today we know that a well-selected drug therapy and proper adjunctive treatment can render myeloma a chronic disease and the quality of life is becoming better and better provided the disease is tackled in a comprehensive manner. Ever younger, professionally and socially active people report to our Foundation while the availability of modern therapies that would allow return to professional work and normal life is strongly limited.
Despite reimbursement of two new drugs in 2019 – carfilzomib and daratumumab – the therapeutic options for Polish patients diverge from the European standards considerably. In addition, these drugs are available in further lines of treatment and in combination with selected drugs only, which leads to the fact that they cannot be administered to a wide group of patients. In their fight for health and life, many patients with myeloma currently have to resort to clinical studies. However, these obviously have numerous limitations as well.

Based on the results of clinical studies and experiences of other countries, we are certain that using modern drugs is necessary to optimise therapy for patients with multiple myeloma. The optimal therapy allows faster return to professional and social activity, reduced time of hospitalisation as well as considerable limitation of costs.

Report purpose

The paramount purpose of this report is to objectively assess the therapeutic options of Polish patients with multiple myeloma. It has been prepared as a comprehensive review according to individual types of therapy, depending on their mechanisms of action. Moreover, the report lists the drugs available in Poland and compares them with European standards to allow an objective review of their availability for therapeutic purposes.

Expert's comments

The report concerning multiple myeloma prepared by the Carita Foundation is a concise and comprehensive summary of the situation of patients with myeloma in Poland. The authors of the report presented epidemiological data and therapeutic options for the treatment of myeloma in the context of registered drugs as well as limitations arising from the fact that numerous molecules are non-reimbursable.

The report points out the imperfections of the data on morbidity and effectiveness of individual therapies of myeloma which we have at our disposal. This is an important voice that should mobilise us to prepare modern registers of multiple myeloma and other oncologic diseases, ones which are lacking in Poland.

The main part of the report constitutes a comparison of the reimbursement of modern anti-myeloma drugs in Poland to that in other European countries. The difference in availability results not only from the fact that some drugs are not reimbursed at all, for instance ixazomib, which due to its oral route of administration would be particularly valuable in the Times of the epidemic, but also due to a strongly limited structure of drug regimens compared to registration indications. The report signals the drugs which should be made reimbursable or the availability of which should be increased as fast as possible. These are, for instance, daratumumab, lenalidomide or carfilzomib in the KD regimen, which according to the ARROW study is administered half as often, which is particularly significant in the face of the epidemic. This mostly results from the analysis of situation of individual populations of patients who took the least advantage of improved access to modern anti-myeloma therapies, which was introduced in 2019. The authors of the report signalled that the future of anti-myeloma therapies will be advanced cell therapies, that is CART.
The report should be a significant voice in the discussion about the further direction of the drug reimbursement strategy for multiple myeloma in Poland.

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Multiple myeloma

Definition

Multiple myeloma develops due to irregularities in the transformation of B cells into plasma cells. Neoplastic transformation of plasma cells results in their uncontrolled proliferation and secretion of high amounts of abnormal immunoglobulins (antibodies). Occurrence of myeloma symptoms is related to excessive concentration of these antibodies.

Epidemiology

Multiple myeloma contributes to 1-2% of all neoplastic cases and 10-15% of cases regarding hematologic neoplasms. It is the third most frequent lymphoid neoplasms after lymphocytic leukaemia and large B-cell lymphoma.

According to the *National Health Fund (NFZ) Report: multiple myeloma*, nearly **2.6 thousand** new cases of multiple myeloma were noted in the public payer system in 2016. That value was slightly higher than the one in the period from 2014 to 2015. The patients were most frequently **females at the age of over 65 years**, but the highest percentage of patients relative to the population size occurred in **males at the age of over 75 years.** Detailed data are presented in the table below.

Year	Number of diagnosed patients (in thousands)	Share of females	Patients' age median	Share of patients below the age of 65	Share of patients at the age of 65-74	Share of patients at or above the age of 75
2016	2.58	54.5%	67	40.1%	30.7%	29.2%
2015	2.57	54.6%	67	40.0%	30.8%	29.2%
2014	2.34	53.1%	66	41.3%	30.0%	28.7%

According to the *NFZ report: multiple myeloma*, nearly **60% (around 1.5 thousand)** of the newly diagnosed patients were treated with chemotherapy dedicated to myeloma. Over a thousand patients (71%) were treated in 2016–2018 with one chemotherapy regimen. 314 patients (21%) were treated with two chemotherapy regimens. The other patients (8%) were treated with three or more chemotherapy regimens. The most frequently administered regimen was VTD: *Bortezomibum*, *Thalidomidum*, *Dexamethasonum*. Out of ca. 2.6 thousand patients diagnosed with myeloma in 2016, 388 had at least one documented service as part of a programme drug dedicated to multiple myeloma in the period from 2016 to 2018.

However, the number seems very much understated as other NFZ data show that there were many more patients treated in the drug regimen with lenalidomide. The data are presented in the table below.

Year	Number of patients with C90.0 diagnosis acc. to ICD-10	Number of patients with C90.0 diagnosis acc. to ICD-10 treated as part of the drug programme entitled "Treatment of patients with refractory or relapsed multiple myeloma	Number of patients with C90.0 diagnosis acc. to ICD-10 treated with the BORTEZOMIBUM active substance
2014	8 560	768 lenalidomide	
2015	9 153	1 078 lenalidomide	
2016	9 546	1 230 lenalidomide	
2017	10 027	1 449 lenalidomide	2 589
2018	10 452	1 655 in total, including 1 627 lenalidomide 67 pomalidomide	2 702
2019*	-		-

* No data for 2019;

Prognosis

There are already effective therapies in the world that allow extending the life of patients with myeloma even by over a dozen years. In Poland, the life of such a patient can be extended by merely 3 to 6 years. To compare, the same patient can live even 20 years in the United States. In Poland, access to new-generation drugs in the therapy of myeloma is limited for instance due to the inclusion criteria of a drug regimen. Moreover, it needs to be stressed that the indicated survival of Polish patients, even to 6 years, does not apply to patients with relapsed disease. In that population, the median of survival is 1.5 years.

In turn, according to the latest NFZ report on multiple myeloma, out of 1.5 thousand patients diagnosed in the period from 2016 to 2018 and treated with chemotherapy dedicated to multiple myeloma, ca. 20% died within a year from the date of the first service provided due to multiple myeloma and ca. 32% did not survive the period of two years. Detailed data are presented in the table below.

patients (in thousands)	% of patients who died within:			
	0.5 year	1 year	1.5 years	2 years
1.5	13.1%	20.1%	26.5%	31.9%

The probability of one-year survival (counted from the date when the first service due to myeloma was provided) for patients treated with chemotherapy dedicated to myeloma is 88% for the patients below the age of 65 years, 77% for the 65-to-74-year-olds and 66% for the patients above the age of 75.

Presentation of drugs available in Europe and new potentially effective therapies

Drugs activating and modulating the immune system

Thalidomide is the drug used for the treatment of multiple myeloma in Europe for the longest time. It is administered in the following cases:

- ✓ in the first line of treatment, as a standard management for patients who cannot undergo autologous stem cell transplantation (ASCT), it is administered in combination with melphalan and prednisone or bortezomib,
  melphalan and prednisone
- ✓ as induction therapy administered in a triplet along with bortezomib and dexamethasone, aiming to improve response before the planned ASCT
- ✓ as maintenance treatment after ASCT, administered in combination with bortezomib and dexamethasone
- ✓ in further lines of treatment, when the previous therapies did not give response

Lenalidomide (Revlimid) was approved by the European Medicines Agency (EMA) in 2007 in the following lines of treatment:

- ✓ for patients who underwent at least one line of treatment: in combination with dexamethasone (RD regimen)
- ✓ for patients with newly diagnosed myeloma who cannot undergo ASCT: in combination with dexamethasone (RD regimen)
- ✓ as monotherapy for patients with newly diagnosed myeloma who underwent ASCT: applied as maintenance treatment

In May 2019, lenalidomide combined with bortezomib and dexamethasone (RVD) was registered by EMA for use in the first line of treatment for patients who do not qualify for ASCT.

Pomalidomide (Imnovid) was approved by EMA in 2013 for use in treatment of adults who underwent at least two lines of treatment with lenalidomide and bortezomib and who suffered from progression of the disease.

Pomalidomide is an effective therapy for relapsed myeloma.

The international Phase 3 MM-003 clinical study showed that patients taking pomalidomide with a low dose dexamethasone were in much longer remission compared to patients treated with one drug – high dose dexamethasone.
Overall survivals (OS) were much longer as well.

In May 2019, pomalidomide combined with bortezomib and dexamethasone (PVD) was registered in Europe for treatment of patients with myeloma who received at least one line of treatment.

Registration of a three-drug regimen based on lenalidomide (RVD) was based in the results of Phase 3 SWOG S07773 study to assess the effectiveness of that therapy in the first line of treatment of myeloma. The study included 525 adult patients with myeloma who were randomly assigned to groups receiving RVD or RD (lenalidomide with dexamethasone). The study results indicated the median of progression-free survival (PFS) is considerably higher in patients treated with the three-drug regimen (RVD) compared to patients treated with the two-drug regimen (Rd, 42 vs 30 months, respectively). The duration and percentage of the response were higher in the three-drug regimen group compared to the two-drug regimen group (52 months vs 38 months and 82% vs 72% of complete responses, respectively).

Registration of a three-drug regimen based on pomalidomide (PVD) was supported by the results of the OPTIMISMM4 study, the first prospective Phase 3 study to assess the three-drug regimen in patients previously treated with lenalidomide, most of whom (70%) were resistant to the drug. The results of the study, where 559 patients undergoing successive lines of treatment after failure of the therapy with lenalidomide (median – two lines of treatment) were monitored, indicated that the three-drug regimen based on pomalidomide (PVD) exhibits a longer PFS than the VD regimen (11.2 months vs 7.1 months, respectively) and lower risk of progression or death (by 39%).

Proteasome inhibitors
Bortezomib (Velcade) has been used in the therapy of myeloma in Europe since 2012. It is administered in the form of intravenous infusions or subcutaneous injections in the following cases:

- ✓ in the first line of treatment, to the patients who cannot undergo autologous stem cell transplantation (ASCT), combined with melphalan and prednisone

- ✓ in the first line of treatment, to the patients before planned ASCT, combined with dexamethasone or as a triple along with dexamethasone and thalidomide
- ✓ in further lines of treatment if the disease progresses, combined with dexamethasone or in monotherapy

Carfilzomib (Kyprolis) in combination with lenalidomide and dexamethasone was approved by EMA in November 2015 for use in the therapy of adult patients with multiple myeloma who underwent at least one treatment regimen before. Subsequently, in June 2016 it was approved in a regimen with dexamethasone only, the so-called KD, also in patients with multiple myeloma who underwent at least one treatment regimen before.

A randomised open Phase 3 study showed that the therapy with the KRD regimen led to the extension of median PFS (progression-free survival) compared to the standard treatment regimen (lenalidomide + dexamethasone), respectively: 26.1 months vs 16.6 months (HR=0.66; 95% CI: 0.55-0.78; one-tailed p=0.001). The 5-year percentage of survival without disease progression or death was 25.6% vs 17.3%, respectively. Moreover, the treatment with the KRD regimen led to significant elongation of median OS (overall survival) compared to the therapy with lenalidomide with dexamethasone, accordingly: 48.3 months vs 40.4 months (HR= 0.79; 95% CI: 0.67-0.95; one-tailed p=0.0045). In the patients who received only one line of treatment before, median OS was by 11.4 months higher compared to the control.

The ENDEAVOR study showed statistically significant lengthening of overall survival (OS) in the patients treated with carfilzomib in the KD regimen (carfilzomib, dexamethasone) with the median being 47.8 months vs 38.8 months (HR=0.76 (95% CI: 0.633-0.915). Significantly, the benefit in terms of overall survival (OS) was observed in all analysed study subgroups. Compared to the standard therapy with the VD regimen (bortezomib, dexamethasone), nearly doubled progression-free survival was achieved (median PFS of 18.7 vs 9.4 months, HR=0.53, p<0.001). The study also confirmed high effectiveness of the KD regimen (carfilzomib, dexamethasone) compared to the VD regimen (bortezomib, dexamethasone) in relation to the percentage of very good partial response (VGPR of 54% vs 29%, respectively) while maintaining a better treatment tolerance (5-time lower percentage of neuropathy compared to the bortezomib therapy). Moreover, it is essential that the KD regimen is as

effective in patients who did not receive bortezomib before and in those who underwent such treatment in the past.

The drug is administered in the hospital setting in the form of intravenous infusions.

Ixazomib (Ninlaro) is the first oral proteasome inhibitor. The drug is effective particularly in patients with the cytogenetic risk, in whom unfavourable prognoses were eliminated.
In November 2016, EMA conditionally approved the three-drug regimen with lenalidomide and dexamethasone in treatment of adult patients with relapsed/refractory multiple myeloma who underwent at least one line of treatment.
The basis for approval was the randomised Tourmaline-MM1 study.

In the randomised Phase 3 TOURMALINE-MM1 study, 722 patients with relapsed or refractory multiple myeloma showed longer progression free-survival (PFS) – up to 20.6 months compared to 14.7 months in the control (p = 0.01), which was expressed by the risk of death or progression reduced by 26% (HR = 0.74, 95%CI 0.59-0.94; p-0.01). A special improvement was exhibited by patients from the high cytogenetic group (del(17p); t(4:14), t(14:16)), median PFS in the ixazomib group was 21.4 months compared to 9.7 months in the group receiving lenalidomide with dexamethasone while the risk of progression or death was reduced by 46% (HR = 0.54, 95%CI, 0.32-0.92; p=0.002). The percentage of treatment response for the median observation period of 14.7 months was 78% and 72% in the two groups, respectively. Response to combination therapy with ixazomib was achieved quickly, the time median was 1.1 months vs 1.9 months in the control (p=0.009). Due to a short observation time, the study did not assess the overall survival of the patients. Additional toxicity related to the addition of ixazomib to the RD regimen was not found, both relative to all adverse reactions as well as severe adverse reactions.

The C16010 China Continuation Study was a complementation of the registration dossier of ixazomib required by the European authorities (EMA). Compared to the main Phase 3 registration TOURMALINE–MM1 study, it pertained to the Far East population (n=115) and included patients in more advanced and prognostically worse stages of multiple myeloma (more patients with refractory myeloma, including myeloma refractory to talidomide, more patients at the ISS3 stage, at the second or third line of earlier treatment with earlier exposure to an immuno-modulating drug). The study showed improvement in progression-free survival (PFS 6.7 vs 4.0 months, HR = 0.598 [0.367-0.972], p=0.035) and over a longer observation period – considerable and significant improvement in overall survival (25.8 vs 15.8 months, HR = 0.419 [0.242-0.726], p=0.001). At the same time, the percentage of therapy discontinuation due to adverse reactions was low and amounted to 11% compared to 14% in the control group (RD).

Histone deacetylase (HDAC) inhibitor

Panobinostat (Farydak)

Approved by the European Commission in 2015, in combination with bortezomibe (Velcade) and dexamethasone, for use in third-line treatment of adult patients with relapsed/refractory myeloma who underwent therapy with bortezomibe and immune-modulating drugs before. The drug is administered in tablet form.

Monoclonal antibodies

Daratumumab (Darzalex) is the first monoclonal antibody to be used in the treatment of multiple myeloma. The drug was conditionally approved by EMA in 2016 as monotherapy for adult patients in whom the disease progressed in the course of treatment with proteasome inhibitors and immune-modulating drugs. Currently, it is authorised for marketing unconditionally.

Daratumumab is registered in the following indications:

- ✓ in combination with lenalidomide and dexamethasone or bortezomib, melphalan and prednisone in the treatment of adult patients with newly diagnosed multiple myeloma who do not qualify for autologous stem cell transplantation

- ✓ in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone, in the treatment of adult patients with multiple myeloma who received at least one therapy before
- ✓ in monotherapy of adult patients with relapsed and refractory multiple myeloma whose earlier treatment included proteasome inhibitor and immune-modulating drug and who showed progression of the disease during the last treatment
- ✓ in combination with bortezomib, talidomide and dexamethasone in the treatment of adult patients with newly diagnosed multiple myeloma who qualify for autologus stem cell transplantation.

In Poland, daratumumab is reimbursable in combination with bortezomib and dexamethasone.

In the randomised open Phase 3 study (CASTOR), an analysis based on a long term of observation showed that after the median observation time of 50 months, treatment with the daratumumab + bortezomib + dexamethasone regimen (DVD) significantly lengthened median PFS compared to the bortezomib + dexamethasone regimen, respectively: 16.7 months vs 7.1 months for the ITT population (HR = 0.31; 95% CI:0.25-0.40; p <0.0001).

Two of the above indications need to be regarded as significant from the vantage point of Polish patients:

Daratumumab with lenalidomide and dexamethasone (DRD) in the treatment of adult patients with multiple myeloma who received at least one therapy before

In the randomised open multi-centre Phase 3 POLLUX study, the median of progression-free survival (PFS) in patients using the DRD regimen was achieved at 44.5 months. The median of overall survival (OS) was not yet achieved in the study. Bearing in mind that the most topical data cover the period of 60 months, overall survival (OS) will exceed that period of time for that regimen.

Daratumumab in combination with bortezomib, talidomide and dexamethasone (D-VTD) in the treatment of adult patients with newly diagnosed multiple myeloma who qualify for autologus stem cell transplantation.

The randomised open multi-centre Phase 3 CASSIOPEIA study proved higher effectiveness of the D-VTD regimen compared to the current

standard treatment of the patients qualifying for stem cell transplantation – the VTD regimen. Due to a high effectiveness of the therapy, the most recently published data covering 30-month observations have not yet allowed to achieve the median of progression-free survival (PFS) or overall survival (OS). 85% of the patients using the D-VTD regimen were free from progression of the disease at month 30 after the therapy start.

Both indications are currently not reimbursable in Poland.

Daratumumab is administered in the hospital setting in the form of intravenous infusions. In this year's June, EMA will register the subcutaneous form of the drug, which will considerably improve the comfort of administration and limit infusion-related complications.

Elotuzumab (Empliciti) – approved by EMA in 2016 for the second line of treatment in a three-drug regimen with lenalidomide and dexamethasone.

Modern therapies
Chimeric Antigen Receptor T-cell therapy (CAR-T) – modern immunotherapy
Europe has one of the highest incidence of multiple myeloma and the patients who underwent several lines of treatment before need new therapeutic options.
Promising treatment options for relapsed and refractory multiple myeloma which can change the natural course of that still incurable disease in the future include genetically modified T cells directed against the antigens present on multiple myeloma cells, e.g. the B-cell maturation antigen (BCMA).
Genetically modified T cells known as CAR-T (chimeric antigen receptor T-cell based therapy) identify and bind to the BCMA antigen on the surface of multiple myeloma. It leads to the destruction of neoplastic cells.

The Horizon 2020 "Caramba" project was launched in Europe in 2018 as a Phase 1/2 clinical study assessing the effectiveness and safety of CAR-T SLAMF7. The European Commission allocated EUR 6.1 million to develop that technology.
The expected effect is the formulation of the algorithm for multiple myeloma treatment allowing making the disease fully recoverable.
Clinical studies are carried out in four neoplasm treatment centres: University Hospital Würzburg (UKW), Ospedale San Raffaele

(Milan), Universidad de Navarra (Pamplona) and the Centre Hospitalier Regional et Universitaire de Lille (Lille).

High hopes put in designs of studies assessing the effectiveness of CAR-T with the application of BCMA are becoming true in the CARTiTUTE Project. Phase 1/2 studies are currently under way. In the world, including several European countries, also in Poland, Phase 3 studies are beginning which use that therapy.

The CAR-T therapies proving to be effective in in vivo studies include: Ide-cel (bb2121), bb21217, JCARH125.
As part of a wide-scale programme of clinical studies by Bristol Myers Squibb i bluebird bio, studies are carried out to assess the effectiveness and safety of modified CAR-T lymphocytes in patients with relapsed and refractory multiple myeloma (e.g. KarMMa, KarMMa-2, KarMMa-3, KarMMa-4, CRB-402b, EVOLVE.)

New immune-modulating drugs.
In the recent years, work has also been carried out on new immune-modulating drug analogues. One of them includes CC-220 (iberomide), which entered Phase 1/2 clinical studies to assess the effectiveness in multiple myeloma, among other diseases. The first reports showed high clinical activity and a beneficial safety profile of that therapy.

Analysis of the situation in Poland – reimbursable drugs and regimens in individual lines of therapy

According to the NFZ report, the chemotherapy regimen most frequently used as the first one in the treatment of patients with newly diagnosed multiple myeloma in the period from 2016 to 2018 was the *bortezomibum*, *thalidomidum*, *dexamethasonum* regimen (VTD).
As to the chemotherapy regimen used as the second one, there was a much higher variety as to the applied treatment regimen, but the *cyclophosphamidum, thalidomidum,dexamethasonum* regimen (CTD) was dominant. Other most frequently used regimens were *bortezomibum, cyclophosphamidum,____dexamethasonum*(VCD) and *melphalanum, prednisolonum*, *bortezomibum* (MPV).

In Poland, we have unlimited access only to thalidomide, an old-generation immune-modulating drug. It is an effective drug, but it is also toxic enough for the European Union and the United States to stop using it nearly altogether. Apart from causing congenital foetal defects, it causes irreversible neuropathy, so it cannot be taken for extended periods of time.

Lenalidomide, second-generation immune-modulating drug which has a lower capacity to cause neurological complications and which is more effective than thalidomide, **is available to Polish patients only in the second line of treatment.** Even patients who do not qualify for ASCT cannot obtain it while in Europe therapy in the three-drug regimen with bortezomib and dexamethasone was recognised as the standard treatment for those patients.
According to experts, the selection of the first line of treatment is essential because over time patients are responding to treatment worse and worse and exhibit shorter periods of remission in further lines of treatment. The application of the RVD regimen in the first line of treatment allows considerable lengthening of the period of first remission in the patients who do not qualify for the transplantation.

As part of effective drug programme B.54. TREATMENT OF PATIENTS WITH REFRACTORY OR RELAPSED MULTIPLE MYELOMA (ICD10 C90.0), patients at the age of 18 years and above who meet at least one of the following criteria are qualified for therapy with lenalidomide:

1) at least two previous treatment protocols were administered before;
2) at least one treatment protocol was administered before and it led to peripheral polyneuropathy of at least 2nd degree if the protocol included thalidomide or of at least 3rd degree if the protocol included bortezomib;
3) it is not planned to transplant marrow stem cells in the patient and bortezomib was administered in the first line of treatment.

Lenalidomide cannot be used in maintenance treatment, which is a standard in most European countries.

Pomalidomide is the latest immune-modulating drug. In Poland, as part of drug programme B.54. it was made available only in November 2018. It is administered in combination with dexamethasone.

The programme includes patients with refractory or relapsed multiple myeloma at the age of 18 years and above who previously underwent at least two treatment regimens covering both lenalidomide and bortezomib and who had a progression of the disease during the last treatment.

Moreover, for continued therapy the drug programme can include patients treated with pomalidomide as part of a different financing method until the drug becomes reimbursable in the drug programme if on the starting date of the therapy, the patients met the eligibility criteria indicated above and simultaneously did not meet the criteria excluding from the programme for safety reasons.

In July 2019, drug programme B.54. TREATMENT OF PATIENTS WITH REFRACTORY OR RELAPSED MULTIPLE MYELOMA (ICD10 C90.0) was expanded with two new drugs: carfilzomib i daratumumab. **In both cases, the reimbursement criteria and programme eligibility criteria were considerably limited.**

In Poland, **carfilzomib** is available for the patients who previously underwent at least one treatment regimen. It is administered solely in combination with lenalidomide and dexamethasone (KRD), solely to patients qualifying for ASCT.
The programme includes patients with refractory or relapsed multiple myeloma at the age of 18 years or above who **meet all of the following criteria:**

1) one, two, or three treatment protocols were applied previously;
2) in any of the previous treatment protocols, bortezomib and/or an immune-modulating drug (thalidomide, lenalidomide or pomalidomide) was used;
3) partial remission was not achieved after 4 cycles according to a protocol including bortezomib or progression was found after at least 3 cycles of treatment with lenalidomide and dexamethasone if it was the last treatment protocol administered to the patient;
4) the patient qualifies for high-dose chemotherapy and hematopoietic stem cell transplantation

Treatment with carfilzomib is continued for a maximum of 8 cycles.

Such narrowed reimbursement indications and very strict programme eligibility criteria dramatically limit access to the drug with confirmed effectiveness to Polish patients.
The narrowing is best exemplified by the number of patients treated with individual drugs in drug programme B.54 in 2019:
– lenalidomide – 1950 patients

– pomalidomide – 411 patients
– daratumumab – 97 patients
– carfilzomib – 59 patients
under Resolution no. 6/2020/III of the NFZ Council of 20.03.2020 on approval of a periodic report on the operations of the National Health Fund for Q42019.

In September 2019, the President of the Agency for Health Technology Assessment and Tariff System gave a positive opinion on the public-fund financing of Kyprolis in combination therapy with dexamethasone for multiple myeloma as part of emergency access to pharmaceutical technologies, which indicates a wider demand than what is stated in the description of the current drug programme and which points to the validity of such treatment.

Carfilzomib is proven to have an effect on significant lengthening of survival of patients, also in a two-drug regimen (KD) currently not reimbursable in the drug programme, but such use of the drug is a standard in most European countries.

According to the presented results of the ENDEAVOR study, overall survival was found lengthened by 9 months (47.8 months vs 38.8 months) with the median of the observation period being 44.3 months in the KD group and 43.7 months in the VD group.
According to the presented data, the median of overall survival for the KD regimen was 47.6 months and for the population of patients using the RD regimen – 40.4 months.

In Poland, as part of drug programme B.54 **daratumumab** is available in the second and further lines of treatment only in the three-drug regimen with bortezomib and dexamethasone (DVD).

The programme enrols adult (≥18 years) patients with relapsed and/or refractory multiple myeloma who meet one of the following criteria:
1) Patients who underwent one line of treatment including bortezomib and marrow stem cell transplantation and it is desirable to provide another therapy with bortezomib according to clinical indications provided there is no peripheral polyneuropathy or neuropathic pain of the 2nd or higher degree;
2) Patients who underwent 2 or 3 previous lines of treatment including bortezomib and lenalidomide.

This year's February The President of the Agency for Health Technology Assessment and Tariff System gave a positive opinion on the public-fund financing of Darzalex (daratumumab) in combination therapy with dexamethasone for recurrent and refractory multiple myeloma as part of emergency access to pharmaceutical technologies.

There is a strong need for allowing Polish patients to undergo therapy in the DRD regimen (daratumumab in combination with lenalidomide and dexamethasone), which is very effective for myeloma and which lengths the progression-free survival to nearly 4 years when administered to patients with relapsed disease.

In addition, daratumumab is registered in three regimens (DRD, DVMP, D-VTD) in the first line of treatment of multiple myeloma and is becoming a standard treatment in the world. Therefore, it will be important to introduce therapy with daratumumab in the treatment of patients with the newly diagnosed disease.

Comparison of the situation in Poland as set against other European countries

Meyloma Patients Europe, an umbrella organisation operating since 2011 which unites foundations and associations for patients with multiple myeloma from 30 countries, presents on its website a report regarding differences in access to treatment in Europe: the European Atlas on Access to Myeloma Treatment. https://www.mpeurope.org/atlas/

In a compilation depicting differences in availability of adopted standard treatments, broken down into individual lines of treatment, Poland had the worst position compared to the countries of the former Eastern Block, even after pomalidomide entered the reimbursement list in 2018. We were outdistanced not only by countries with a slightly higher per capita income: Estonia, Slovakia, Lithuania and the Czech Republic, but also countries with a much lower per capita GDP such as Romania, Hungary and Bulgaria.

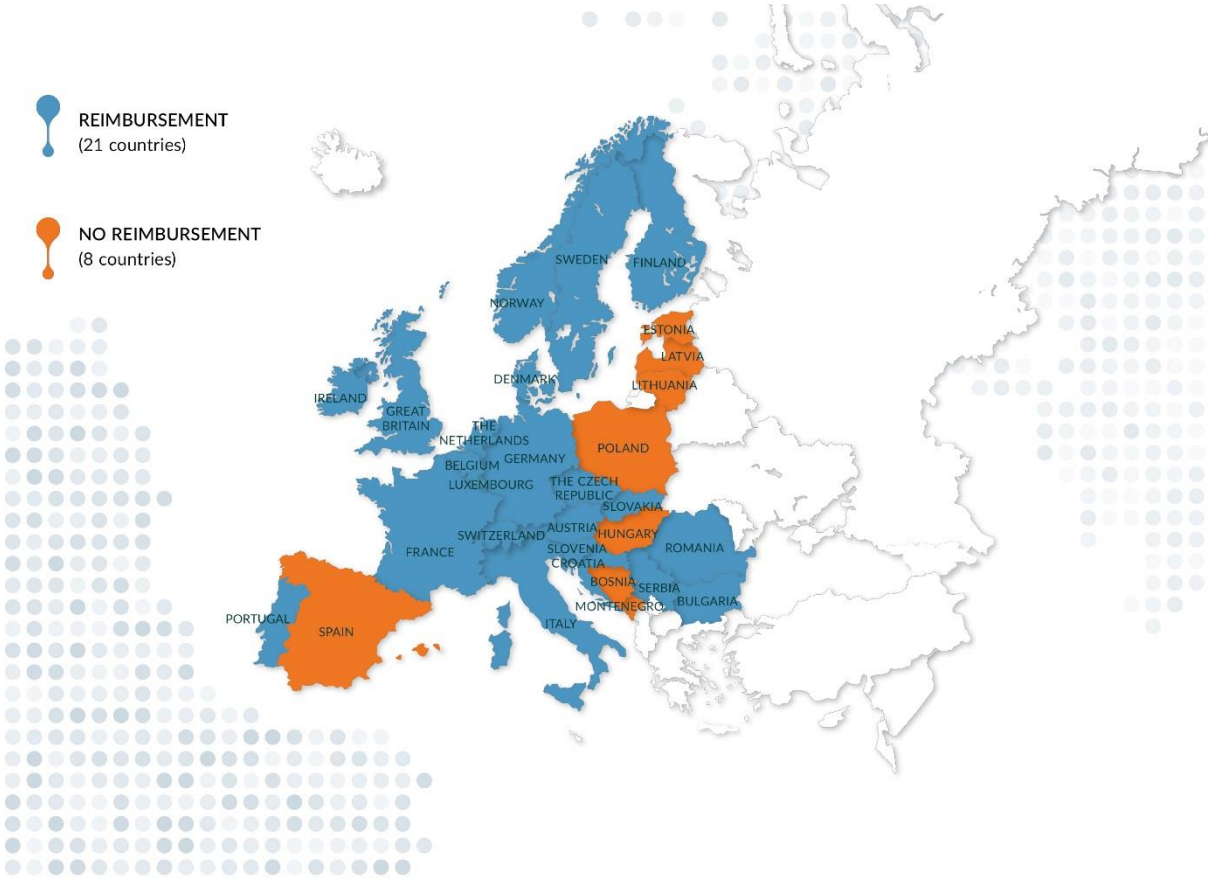
The gap between Poland and the countries of the European Union is shown in the table below.

Molecule name	Indications in the treatment of multiple myeloma	EU	Poland
Thalidomide	The first and successive lines of therapy	2008	2008/2012
Bendamustine	The first and successive lines of therapy	2010	2014/2015
Lenalidomide	• Monotherapy for patients with newly diagnosed myeloma who underwent ASCT applied as maintenance treatment. • Patients with newly diagnosed myeloma who cannot undergo ASCT – drug administered in the RD regimen • Relapse or refractoriness after at least one line of therapy – drug administered in the RD regimen • First line of treatment in the patients who are not candidates for ASCT, administered in the three-drug regimen with bortezomib and dexamethasone	2007 2019	none none 2010/2014 none
Pomalidomide	• Previously at least two lines of treatment, including treatment containing lenalidomide and bortezomib, plus signs of progression during the last line of treatment * * In Poland, administered with dexamethasone only • Second line of treatment in the three-drug regimen with bortezomib and dexamethasone	2013 2019	2018 none
Bortezomib	• First line of treatment administered in two- and three-drug regimens with dexamethasone and thalidomide • In further lines of treatment if the disease progresses, combined with dexamethasone or in monotherapy	2012	2015
Carfilzomib	In combination with lenalidomide and dexamethasone (KRD) or only dexamethasone (KD), it is indicated for treatment of adult patients with multiple myeloma who underwent at least one treatment regimen* * In Poland reimbursable only in the KRD regimen in the patients qualifying for treatment with high-dose chemotherapy and hematopoietic stem cell transplantation	2015 – KRD regimen 2016 – KD regimen	2019 – KRD regimen none – KD regimen
Ixazomib	Second and further lines of treatment in the three-drug regimen with lenalidomide and dexamethasone	2016	none
Panobinostat	Previously at least two lines of treatment, including ones containing bortezomib and immune-modulating drugs, recommended in combination with bortezomib and dexamethasone	2015	none
Daratumumab	• Monotherapy of the patients who did not respond to treatment with proteasome inhibitors and immune-modulating drugs. • First line of treatment in the three-drug regimen: lenalidomide or bortezomib and melphalan plus dexamethasone, for the patients who are not candidates for ASCT • First line of treatment in the three-drug regimen with bortezomib/thalidomide plus dexamethasone for the patients qualifying for ASCT • Second line of treatment + in the three-drug regimen: lenalidomide plus dexamethasone • Second line of treatment + in the three-drug regimen: bortezomib plus dexamethasone *	2016	none none none none 2019

	* In Poland, for the patients after ASCT for whom therapy with bortezomib is justifiable		
Elotuzumab	Second line of treatment in the three-drug regimen with lenalidomide and dexamethasone	2016	none

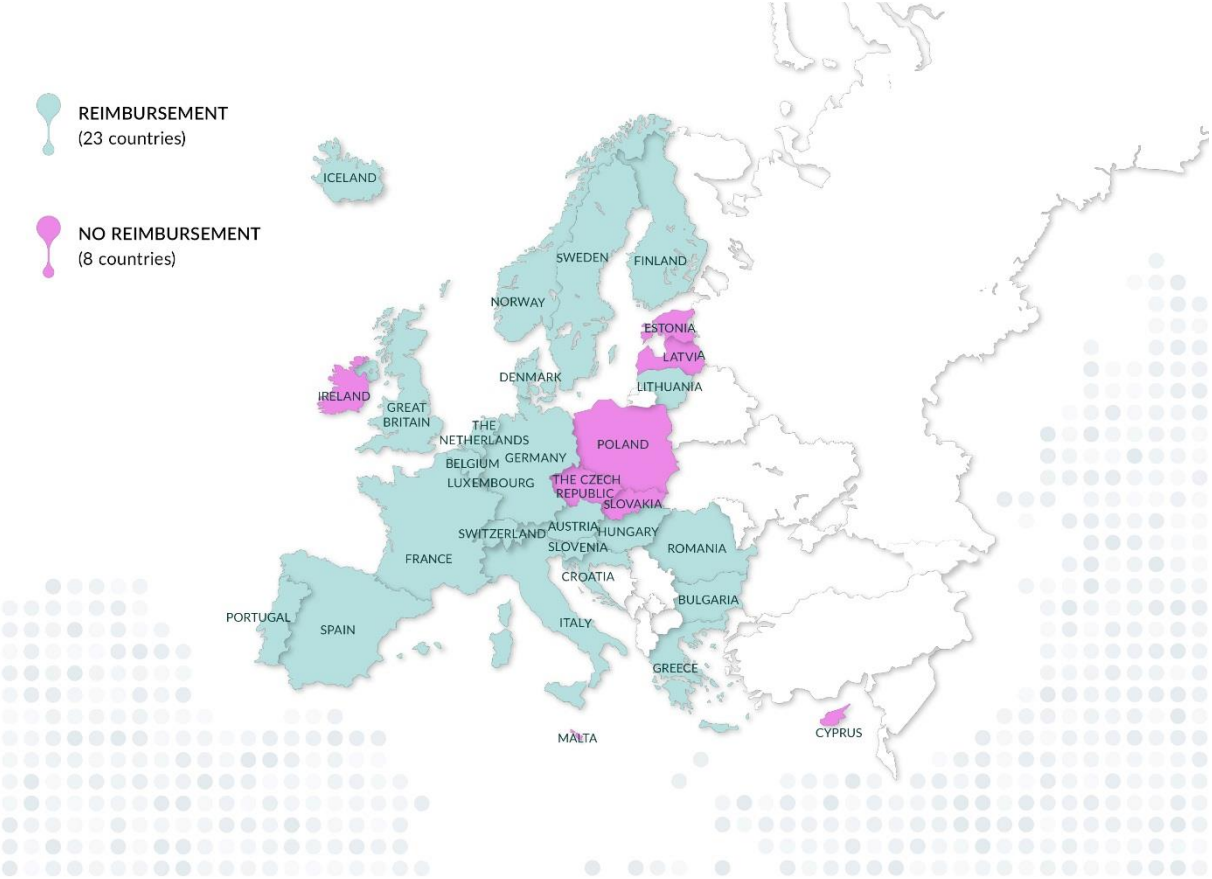
Three out of eight modern molecules indicated in therapy for myeloma are still unavailable to the Polish patient: Panobinostat, Elotuzumab and Ixazomib.

Ixazomib (Ninlaro) – in combination with lenalidomide and dexamethasone, it is indicated for treatment of adult patients who underwent at least one treatment regimen previously. Based on the information provided by the drug manufacturer, Ninlaro is reimbursable in 21 countries. See the image above.

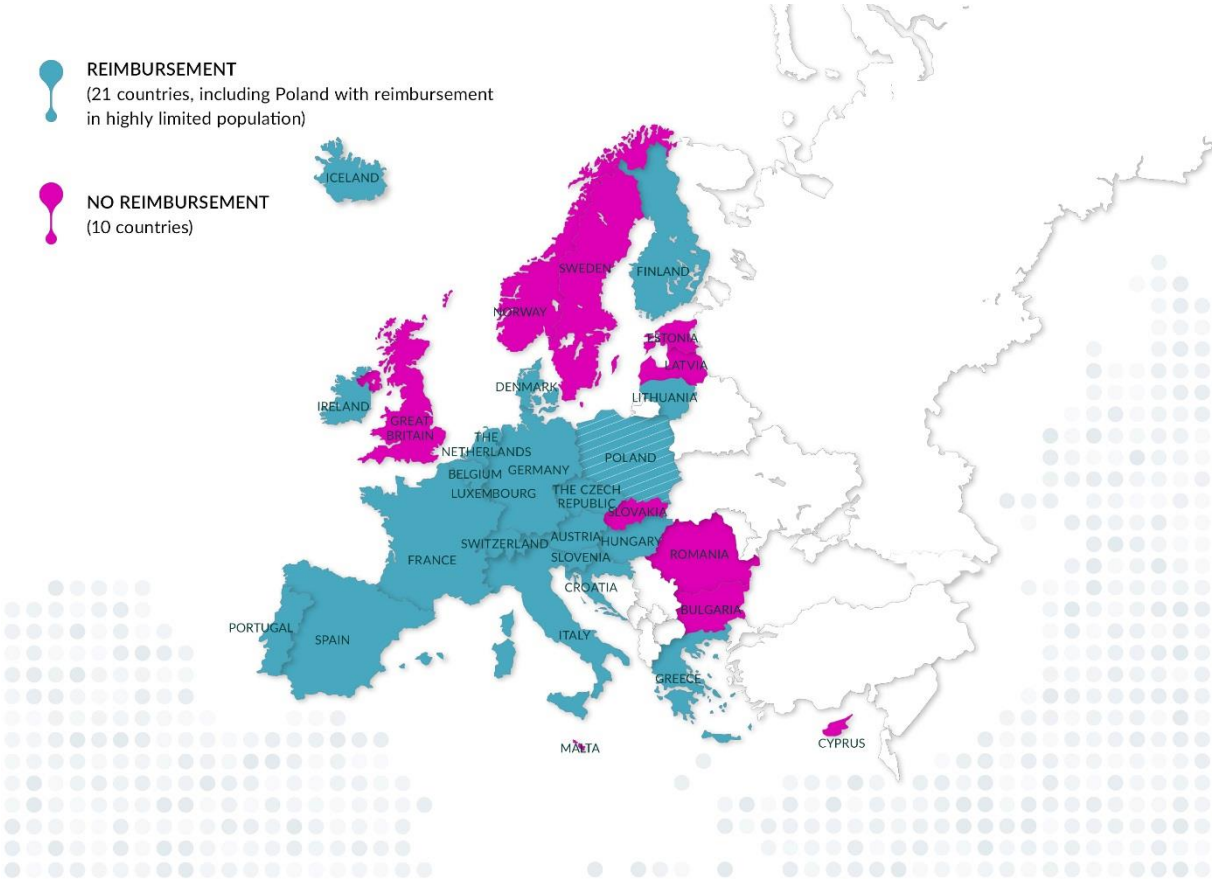

REIMBURSEMENT
(21 countries)
NO REIMBURSEMENT
(8 countries)
SWEDEN
FINLAND
NORWAY
ESTONIA
LATVIA
LITHUANIA
DENMARK
IRELAND
GREAT BRITAIN
THE NETHERLANDS
POLAND
BELGIUM
GERMANY
LUXEMBOURG
THE CZECH REPUBLIC
SLOVAKIA
AUSTRIA
HUNGARY
SWITZERLAND
FRANCE
SLOVENIA
ROMANIA
CROATIA
BOSNIA
SERBIA
MONTENEGRO
BULGARIA
PORTUGAL
SPAIN
ITALY

The data presented by the manufacturer of the Revlimid drug suggest that only four European countries, including Poland, cannot use lenalidomide in maintenance treatment of adult patients with newly diagnosed multiple myeloma after autologous stem cell transplantation and in treatment of adult patients with previously untreated multiple myeloma who do not qualify for ASCT. See the image above.

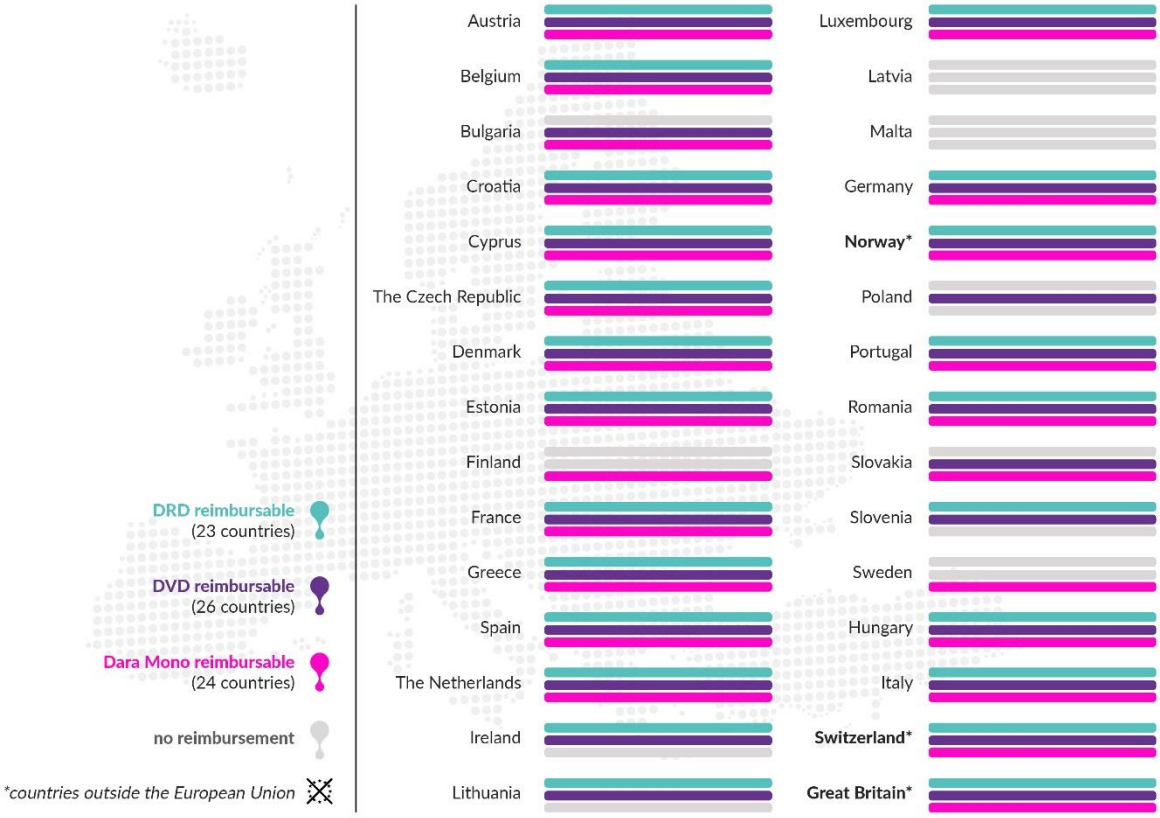
The information furnished by the Kyprolis drug manufacturer indicates that the KD regimen, unavailable in Poland, is reimbursable in 23 European countries. See the image above.



However, among 21 European countries where the KRD regimen is reimbursed, only Poland has such significantly limited eligibility criteria. See the image above.



In the vast majority of European countries, Darzalex is reimbursable in all basic regimens: DVD, DRD and monotherapy. See the image above.



To sum up, the key conclusion drawn from the presented data is the fact that access to innovative therapies used to treat multiple myeloma is suboptimal in Poland. Access to drugs deviates not only from the drug reimbursement standards of the countries of Western Europe (e.g. Germany or France). Polish patients have a more restricted access even into comparison to countries from Central and Eastern Europe. Patients from such countries as the Czech Republic, Hungary or Slovakia, but also from Baltic countries, have a freer access to pharmacotherapy – which

obviously translates into longer survival of patients with multiple myeloma. The situation requires urgent improvement.

It needs to be emphasised here that the report prepared by the Institute of Healthcare Management of the Lazarski University entitled "Costs of new pharmaceutical technologies in the treatment of the most commonly diagnosed neoplasms Prognosis 2019-2021" indicated in the part concerning multiple myeloma the following treatment regimens as requiring financial support from the state treasury:

Daratumumab (DVD three-drug regimen)	Treatment of adult patients with relapsed and refractory multiple myeloma whose previous treatment included a proteasome inhibitor and an immune-modulating drug was unsuccessful
Daratumumab (D-VMP, DRD or D-VTD regimen)	Treatment of patients with newly diagnosed multiple myeloma.
Daratumumab (DRD three-drug regimen)	Treatment of adult patients with multiple myeloma who received at least one therapy previously.
Carfilzomib (KRD three-drug regimen)	Treatment of patients with relapsed and refractory multiple myeloma
Carfilzomib (two-drug KD regimen)	Treatment of relapsed and refractory myeloma in the patients who were administered at least one treatment regimen.
Ixazomib (IxaRD three-drug regimen)	Treatment of patients with multiple myeloma who have already undergone at least one treatment regimen.
Pomalidomide (three-drug regimen in combination with bortezomib)	Treatment of relapsed and refractory myeloma in the patients who were administered lenalidomide previously.

Panobinostat (PanoVD three-drug regimen)	Treatment of patients with relapsed and refractory multiple myeloma (third and further lines of treatment)
Elotuzumab (EloRD three-drug regimen)	Treatment of patients with multiple myeloma who have already undergone at least one treatment regimen.
Lenalidomide	Maintenance treatment for patients with multiple myeloma after autologous stem cell transplantation

As at the date of this report, the following medicinal products are in the process of inclusion in the reimbursement programme:

- Kyprolis (carfilzomib) in the drug programme entitled: "Treatment of patients with refractory or relapsed multiple myeloma with cartilzomib," in the two-drug KD regimen
- Ninlaro (ixazomib) in the drug programme entitled: "Ixazomib in treatment of patients with refractory or relapsed multiple myeloma," in the three-drug regimen with lenalidomide and dexamethasone.
- Revlimid (lenalidomide) in the drug programme entitled: "Lenalidomide in treatment of adult patients with previously untreated multiple myeloma."

At the same time, in connection with the Act of 31 March 2020 on amendment to some statutes regarding the healthcare and connected to preventing, counteracting and fighting COVID-19, the dates of the above inclusion procedure are suspended until this year's 31 August. The minister competent for health affairs can, however, take any action aiming to issue administrative decisions specified in the Act of 12 May 2011 on reimbursement of drugs, foodstuffs of special nutritional purposes and medical devices.
Therefore, efforts must be made for such decisions, taking into account the needs of patients with myeloma, to be taken.

Summary

Myeloma is a disease that we – the patients – do not deserve. Observing the survival status of patients from other countries of Europe, we are sure that myeloma is a disease that does not exclude an active life of good

quality provided it is treated properly. We give a fight, we want to live as long as possible, come back to work as quickly as possible and fulfil our social roles. We can achieve it only thanks to access to modern therapies with the support of the Polish state. Our life with myeloma is also an investment and we would like it to be seen like that.

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Dictionary of selected abbreviations

VTD: Bortezomibum, Thalidomidum, Dexamethasonum

RD: Lenalidomidum, Dexamethasonum

RVD: Lenalidomidum, Bortezomibum, Dexamethasonum

PVD: Pomalidomidum, Bortezomibum, Dexamethasonum

KD: Carfilzomib, Dexamethasonum

KRD: Carfilzomib, Lenalidomidum, Dexamethasonum

VCD: Bortezomibum, Cyclophosphamidum, Dexamethasonum,

CTD: Cyclophosphamidum, Thalidomidum,Dexamethasonum,

MPV: Melphalanum, Prednisolonum, Bortezomibum

VD: Bortezomibum, Dexamethasonum,

DVD: Daratumumab, Bortezomibum, Dexamethasonum,

D-VTD: Daratumumab, Bortezomibum, Thalidomidum, Dexamethasonum

ASCT: autologous stem cell transplantation,

EMA: European Medicines Agency,

IRD: Ixazomib, Lenalidomidum, Dexamethasonum