RESEARCH REPORT

The Societal Impact of Lenalidomide

HEALTH EFFECTS AND WIDER SOCIO-ECONOMIC EFFECTS OF A MEDICAL INNOVATION

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1 Introduction and background

1.1 Introduction

Worldwide, there are ongoing debates on the reimbursement of drugs within health care systems. Demographic changes (i.e. increasing longevity) as well as changes in the relative prevalence of diseases challenge many healthcare systems. While less people are dying from infectious diseases, non-communicable and chronic diseases are on the rise. At the same time, recent pharmaceutical breakthroughs have significantly improved treatment options for many chronic and severe diseases. These developments have led to rising concerns about increasing costs leading to restricted access to these innovative medicines. Thus, in a landscape with high competition for limited healthcare resources, healthcare systems are increasingly urged to base spending decisions on the overall value that drugs bring to patients and to the society.

However, to date, there exists no generally accepted definition of value in this context. Recently, an increasing number of researchers and policymakers focus on this topic. Many argue that the value of medical innovations goes beyond a mere clinical benefit and that this should be taken into account in assessing the value of medical innovations [1], [2]. While quality adjusted life years (QALYs) – or similar measures – are core elements of value that are generally considered in all value assessments, other elements are less common and only inconsistently considered [2], [3].

One important value dimension, which is – although required by many health technology assessment (HTA) bodies – only occasionally considered, are the effects of health on labor productivity as well as productivity outside of the labor market. Main reasons for not taking these into account are challenges in measuring productivity gains but also the notion that especially labor productivity applies only to patients who are active in the labor market and thus undervalues health benefits for elderly [3].

Further, there are dimensions that are being discussed as important elements of value but are not typically included in official HTAs or other value assessments. These include the *insurance value* or *value of reduction on uncertainty* (i.e. the reduction of risk of becoming sick and risk of suffering from a severe disease), the *value of hope* (i.e. the value of knowing that innovative technologies might bring better treatment option, cure, etc.), or the *real option value* (life extending medications *de facto* offer opportunities of

benefitting from future innovations, e.g. CAR-T[1]). Also, medical innovations often trigger scientific spillovers: Knowledge in one area may lead to the development of further valuable drugs (e.g. CAR-T, combination therapies, new indications) [2], [4].

In this study, we assessed the value of one innovative drug in oncology considering both the health benefits *and* socio-economic benefits that result from this improved health. These socio-economic benefits include productivity effects in paid and unpaid work as well as a societal value of life captured by the *value of a statistical life year* (VSLY).

First, we quantified the health benefits of using lenalidomide (including both Revlimid® and possible future generics) as measured in progression-free survival (PFS) and overall survival (OS) in the treatment of multiple myeloma. That is, we quantify the additional health benefits that can be gained if lenalidomide is used instead of the comparator treatment that would otherwise be applied in a "world without lenalidomide". The respective comparator treatment for each treatment line was determined in consultation with Celgene and based on approved treatment options that were available at the time of the analysis (06/2017).[2]

Second, we quantified the productivity effects that are induced by this longer PFS in Germany. Regarding productivity effects, we considered productivity in paid as well as unpaid work. Further, we considered both the benefits that have been attained since the introduction of the drug in 2007 and the benefits that can be gained from now up to the year 2030. With the quantification of the intrinsic value of life by applying the VSLY, we complement the health benefits and productivity effects. This provides a comprehensive view on different dimensions of the value of a medical innovation.

1.2 Multiple myeloma: Etiopathology and treatment options

Multiple myeloma has a progressive pathology and is eventually fatal. The disease is caused by malignancy of blood plasma cells, which, at later disease stages, show high bone osteolytic activity leading to extensive skeletal destruction.

Multiple myeloma tends to have a rare prevalence and an onset in rather later stages of life. The mean age of MM patient in Europe is 73 years [5]. The annual incidence median

[1] T-cells that are genetically engineered to produce an artificial T-cell receptor ("Chimeric Antigen Receptor T-cells").

[2] At the time of the finalization of this report (May 2020), there have been approved further treatment options. These are not considered in the calculations of this project.

in Germany is 5.4 cases per 100,000, being slightly higher in males (5.85) than females (5.06 per 100,000) [6].

In the last two decades, breakthrough therapy options have become available altering the rate and severity at which the disease develops. In such a way, multiple myeloma has changed from a disease with an abrupt fatal course to one with chronic, therapeutically controllable progression rate. Cure from MM is still very rare and tumor relapse is almost inevitable after a variable duration under the provided therapy. Nevertheless, patients can benefit from often relatively long progression-free survival phases in which the tumor is well controlled. Under Darwinian mechanisms, the few tumor cells that do not respond to treatment from the beginning replicate and eventually give rise to a relapsed, treatment-refractory form of multiple myeloma (rrMM). At this stage the patient is switched by the treating physician to a new therapy option. Therefore, the three clinical parameters of highest relevance to the disease picture are: Response to therapy, progression-free survival, and overall survival.

2 The Health Footprint

2.1 Methodology

The starting point for the quantification of the Social Impact are the positive health effects that an innovative medicine brings to the patients suffering from a specific disease. With the health footprint, we calculated incremental health benefits that a treatment with lenalidomide generates compared to an alternative treatment with the next best available therapy option.

We considered the benefits of using lenalidomide in all therapy lines in multiple myeloma for which its use was authorized at the time of analysis (06/2017). This includes the use of lenalidomie (a) as maintenance monotherapy in adults who have had an autologous stem cell transplantation; (b) as first line of therapy in combination with either dexamethasone or melphalan and prednisone for the treatment of adults with previously untreated multiple myeloma, who cannot have a stem cell transplantation; and (c) in combination with dexamethasone in adults who have relapsed after being treated with one or more prior treatments, relapsed refractory multiple myeloma (rrMM) [7].

In order to calculate incremental health benefits, we simulated the treatment course and treatment outcomes of MM patients in alternative treatment scenarios. In the first scenario, all patients are treated with lenalidomide (mono or combination therapy – depending on the treatment line). In the other scenario, all patients are treated with the best alternative therapy option. This best alternative treatment option was defined in consultation with Celgene und refers to the point of time when the analysis was conducted (06/2017). Therefore, the patient population in our model is defined as patients who have been treated with a lenalidomide-based therapy for multiple myeloma in the past; or those who are expected to be treated with lenalidomide in the future according to market penetration forecasts. The population was furthermore stratified into sub-cohorts by age and gender. The proportional size of each of the sub-cohorts was based on published epidemiological data on prevalence and incidence[8]. The health outcomes of our study were quantified as overall survival (OS) and progression-free survival (PFS) patient-years.

For each treatment line in which lenalidomide is approved, we constructed a dynamic population model that depicts prevalence and incidence developments in the population of interest and simulates the relevant health outcomes (PFS and OS) for the entire patient population. The population model is based on two Markov models with two

different discrete health states each: One model quantifies the PFS years, while the other depicts the OS years. The transition probabilities for the Markov models were derived from Kaplan-Meyer curves in published studies on clinical trials assessing the effectiveness of the respective treatments. Since there are typically no numerical data in addition to graphical displays, the WebPlotDigitizer[3], a method to extract data from graphs, was used [9]. The digitized survival data from the clinical trials were further fitted and exponentially parametrized to derive constant transition probabilities between different health states for the 28-day cycles that were used to model the PFS and OS developments.

2.1.1 First line therapy (L1)

Lenalidomide has been approved since 2015 in combination with dexamethasone (Rd) for the treatment of adults with previously untreated multiple myeloma, who are not eligible for a stem cell transplantation. In order to define the comparator treatment for our analysis, we assessed which alternative treatments were available in a "world without lenalidomide", i.e. if all treatment options that include lenalidomide are no longer available. Typically, the first line treatment is based on immunomodulating drugs (e.g. lenalidomide) or on proteasome inhibitors (e.g. bortezomib). In a world without lenalidomide, the best alternative treatment option would thus be a bortezomib-based regime. In order not to overestimate the incremental benefit of a treatment with Rd, we assigned the most effective bortezomib-based treatment, which is a combination of bortezomib, melphalan, and Prednisone, as our comparator treatment.

Since no head-to-head trials were conducted to compare Rd to VMP, the transition probabilities for the Markov model were derived from an adjusted indirect comparison conducted for Celgene based on the results from the FIRST and VISTA clinical trials[10]. PFS and OS hazard rates were derived from the exponentially fitted and extrapolated curves of the published Kaplan-Meyer curves.

The patients were defined as those who received a treatment since the market authorization in 2015 or for whom a treatment with Rd is expected according to market penetration estimations. Estimations of the relevant patient population are based on extrapolations of administrative data on incidence rates, total population forecasts,

[3] The program is used in four steps. First, the image of a graph needs to be uploaded. The second step is calibrating the axes by assigning two points of known values on each axis. Then, the next step in manual mode is adding data points by clicking on the graph out of which WebPlotDigitizer calculates the precise coordinates of each point. Finally, the data can be exported in e.g. a csv file.

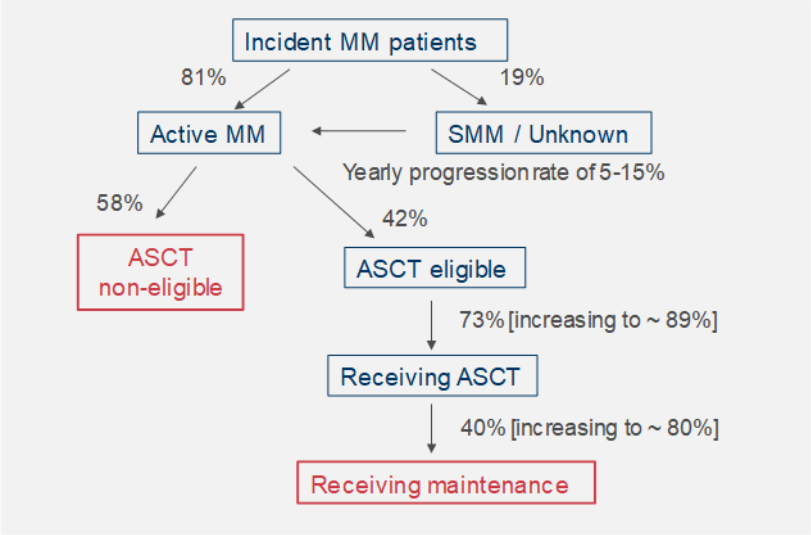
lenalidomide market share data, and on typical treatment courses of MM patients (see Figure I).

The specific assumptions for the L1 scenario were that all patients who receive a lenalidomide-based treatment receive the doublet combination Rd (either brand or generic lenalidomide). The share of lenalidomide-based treatment was assumed to increase in first line treatment throughout time. The availability of newer generation innovative therapies that allow for the so-called triplet regimens (e.g. DRd) from 2020 onwards were neglected (conservative assumption).

Since older patients are less eligible to receive stem cell transplantation, we assumed the following patient shares per age group to be ineligible for stem cell transplantation (and thus to receive a L1 therapy without ASCT):

- 5% of patients in age-group 20-39
- 20-30% of patients in age-group 40-69
- 70% of patients in age-group 70-79
- 90% of patients in age-group>80

Figure I: Relevant patient populations for different first line therapies: ASCT non eligible patients and ASCT eligible patients (receiving ASCT & maintenance after ASCT)



Source: [8], [11], Celgene internal data.

2.1.2 Maintenance therapy

Furthermore, lenalidomide has been approved for maintenance treatment after a stem cell transplantation since 2017. As there are no other -officially authorized- options for maintenance treatment, our comparator treatment is placebo. Since our aim was to model the effects of the use of lenalidomide until 2030, we implicitly assumed that there will also be no other treatment options for maintenance in the future.

Transition probabilities for the Markov model for maintenance therapy were derived from a meta-analysis conducted by McCarthy et al. (2017) based on different clinical trials (CALGB 100104, IFM 2005-02, and GIMENA RV-MM-PI-209) [12]. PFS and OS hazard rates were likewise derived from the exponentially fitted and extrapolated curves of the published Kaplan-Meyer curves.

Eligibility for stem cell transplantation in MM generally varies across countries and institutions. In most European countries, transplantation for myeloma is offered primarily to patients younger than 65 years of age and only in rare cases to older patients [13]. We thus assumed the following regarding eligibility for stem cell transplantation per age group:

- 95% of patients in age-group 20-39
- 70-80% of patients in age-group 40-69
- 30% of patients in age-group 70-79
- 10% of patients in age-group>80

2.1.3 Later line therapies (L2+)

In 2007, lenalidomide, in combination with dexamethasone, received the first label approval for second and later lines of therapy in adults who have had one or more prior treatments. As in first line therapy, later line therapies are typically based either on immunomodulating drugs (e.g. lenalidomide) or on proteasome inhibitors (e.g. bortezomib). The therapeutic class of the first line treatment regimen largely determines the choice of the subsequent line of therapy. After the relapse following a bortezomib-based first line therapy, a lenalidomide-based regimen is usually chosen as second line, and vice-versa. Thus, in second line treatment, lenalidomide is indicated for those patients who had bortezomib as first line treatment. In a hypothetical world without lenalidomide, bortezomib is consequently not to be considered as an option in second line treatment (as it has been already administered in first line therapy and thus relapsed patients have developed resistance to such therapy). In the common clinical practice, retreatment with a combination containing one or more active ingredients that failed in attaining response in a previous therapy line is sometimes considered by the treating physician. For data availability and practicality purposes, however, retreatment was not considered as an option in our model.

Therefore, high dose mono dexamethasone (HD Dexa) therapy was assumed to be the best feasible alternative therapy and was used as the comparator treatment in our L2+ analyses. Although these days HD Dexa may not be any longer considered a realistic alternative treatment option, we still argue that it is a reasonable assumption within our overall model. First, at the time of approval in 2007, HD Dexa was indeed an alternative treatment option for patients in second line with prior exposure to thalidomide or bortezomib. Using it as comparator in our analyses thus underlines the huge medical

advances in the treatment of MM that can be attributed to the development of several effective drugs in the last two decades, among them lenalidomide. Second, considering bortezomib, for instance, as comparator in further line treatments would entail the assumption that it is not an option as prior first line treatment. This, in turn, would then have to be taken into account in the set-up of the overall model, requiring another comparator in first line treatment.

As for L2+ treatment, several new active ingredients provided in triplet combination therapies including lenalidomide have made it to the market in the last few years. These triplets lead to clinical benefits that are superior to the conventional doublet therapy with Rd. We considered this additional benefit in our analysis by assuming that a certain proportion of the relevant patient population will be treated with daratumumab + Rd (DRd), elotuzumab + Rd (ERd), carfilzomib + Rd (KRd), or ixazomib + Rd (NRd).

Transition probabilities for the Markov model for the second line therapy were derived from the following clinical trials: MM-09 [14], ASPIRE [15], POLLUX [16], ELOQUENT-2 [17] and TOURMALINE [18]. Again, PFS and OS hazard rates were derived from the exponentially fitted and extrapolated curves of the published Kaplan-Meyer curves. Curves were compared through the Rd bridge comparator in an unadjusted indirect comparison.

Further assumptions regarding the second line therapy were:

- Decreasing share of lenalidomide based treatments in patients with relapsed/refractory MM as lenalidomide becomes increasingly indicated for first line therapy
- For calculations: All patients who receive a lenalidomide based treatment receive either Rd or one of the four new triplets DRd, KRd, IxaRd or EloRd (or generics of it)
- Distribution of patients over age groups is assumed to be identical to age distribution of newly diagnosed patients, considering that patients should be on average 2 years older

Table I: Main input parameters for the calculation of the health footprint

	Response rate	PFS probability per cycle	OS probability per cycle	Survival curvefitting	Reference
Rd (L1)	0.750	0.977	0.99	exponential	[10]
VMP (L1)	0.710	0.979	0.994	exponential	[10]
R mono (Maint.)	--	0.988	0.995	exponential	[12]
Placebo (Maint.)	--	0.976	0.993	exponential	[12]
Rd (L2+)	0.650	0.955	0.989	exponential	[14]
DRd (L2+)	0.930	0.985	0.993	exponential	[16]
KRd (L2+)	0.870	0.950	0.988	exponential	[15]
EloRd (L2+)	0.790	0.965	0.988	exponential	[17]
IxaRd (L2+)	0.780	0.968	0.911	exponential	[18]
HD Dexa (L2+)	0.280	0.861	0.973	exponential	[14]

2.2 Results

In the following, we present results for the health footprint separately for each therapy line. Figure II depicts aggregate PFS and OS for the two first line treatment scenarios by year and age group. The use of Rd in the first line therapy leads to an overall 35,304 PFS years over the years 2015 to 2030. Treatment with VMP, on the other hand, leads to only 27,643 PFS years. Therefore, there is a difference in PFS of about **7,661** years.

Furthermore, the use of Rd in the L1 therapy leads to about 66,100 OS years (vs. 56,339 for the treatment with VMP). The difference in OS is **9,761** years.

Figure II: PFS and OS years in first line therapy, per age group

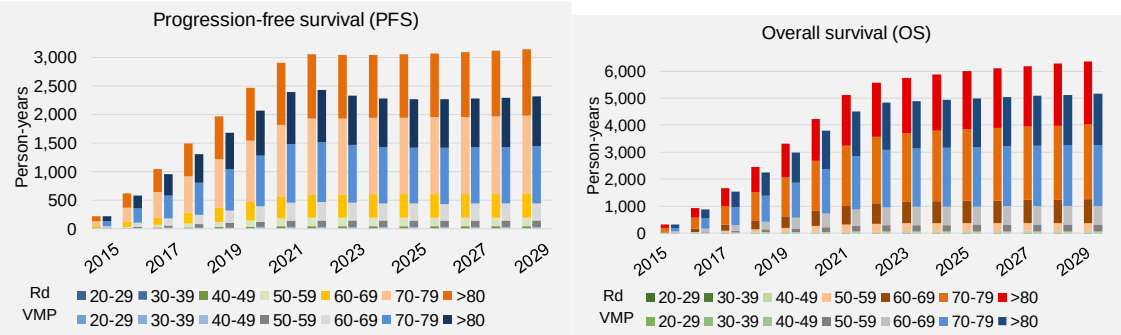


Figure III summarizes results for the two scenarios in maintenance therapy: The use of R mono in maintenance therapy leads to an overall of 55,086 PFS years over the years 2017 to 2030 (vs. 37,426 for the treatment with placebo). The difference in PFS is 17,660 years.

Furthermore, the use of R mono in maintenance therapy leads to about 70,116 OS years (vs. 64,587 for the treatment with placebo). This results in a difference in OS of about 5,529 years.

Compared to the first line treatment scenarios, in maintenance therapy, the share of PFS and OS years that can be gained in younger age groups are relatively higher. This is due to the fact that maintenance therapy is given to those patients who previously received an ASCT. As stated in the previous section, these are typically younger and healthier patients.

Figure III: PFS and OS years in maintenance therapy, per age group

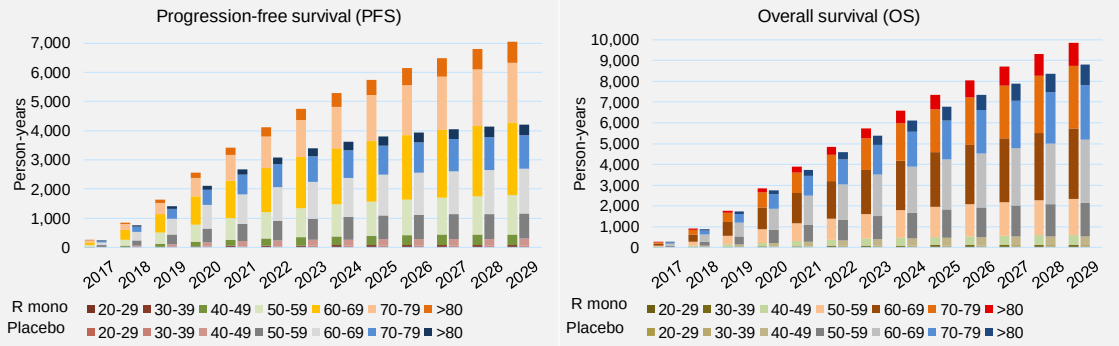
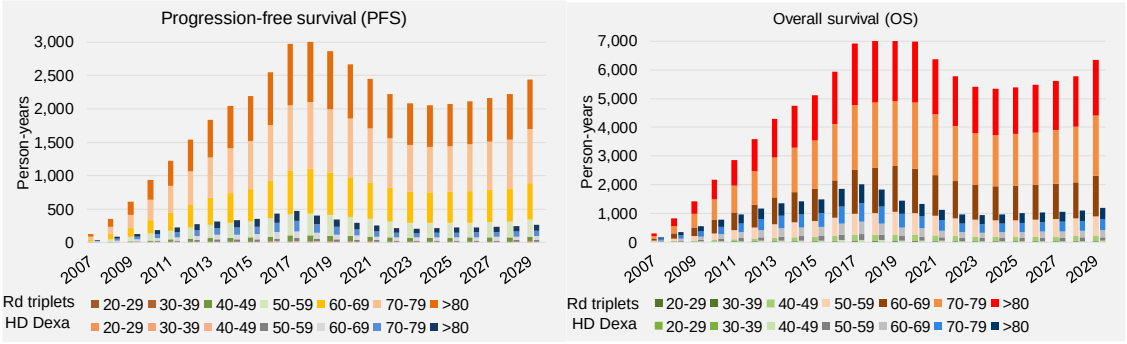


Figure IV depicts PFS and OS years that result from the treatment of patients in later treatment lines with Rd (and different combinations of Rd triplets) and HD Dexa, respective. The use of Rd and R triplets in L2+ therapies lead to an overall of 44,750 PFS years over the years 2007 to 2030 (vs. 6,005 for the treatment with HD Dexa). The difference in PFS amounts to about 38,745 years.

Furthermore, the use of Rd and R triplets in L2+ therapies lead to about 107,609 OS years (vs. 24,176 for the treatment with HD Dexa). This results in a difference in OS of about 83,433 years.

Both aggregate PFS and OS gains are considerably higher for the L2+ therapies, compared to L1 and maintenance therapy. First, since lenalidomide was approved for second line treatment in 2007, the overall number of years that are taken into account is higher (2007-2030). Second, the comparator treatment, HD Dexa, is clearly less effective that any combination including lenalidomide. The appropriateness of HD Dexa as comparator might generally be challenged, the overall set-up of this study, however, warranted this choice (see also previous section on methodology and discussion part below).

Figure IV: PFS and OS years in later line therapies (L2+), per age group



3 The Socio-economic Footprint

3.1 Methodology

With the socio-economic footprint, we quantified the economic gains that come along with the improved health outcomes as derived in the previous section. Longer time spent in a progression free health state implies that during this time, patients are better able to pursue their jobs (paid work) as well as their daily domestic work (unpaid work). Economic gains thus stem from higher labor productivity in the progression free health state as compared to when a disease progression sets in.

One important assumption in comparing different medical treatments is that the average productivity while in either health state is the same for all treatment options. The difference in economic gains thus depends only on the length of the progression free period.

In quantifying these economic gains, we considered not only paid but also unpaid work. Besides employment, individuals also perform household activities for which they receive no payment. Several studies have found that often non-market household activities, referred to as unpaid work, account for a significant portion of output [19]. They thus contribute to a society's prosperity by generation of value added. Therefore, although this output is generally not captured in the System of National Accounts, which calculates the overall productivity of a nation, it constitutes a relevant welfare contribution to a society [19], [20]. We argue that it is crucial to also take these productivity gains into account when quantifying the socio-economic effects of a drug. Considering only paid work would underestimate the welfare contribution of unpaid work within a society.

3.1.1 Paid work

In order to quantify the productivity gains from paid work, we had to estimate the average employment and work capacity of multiple myeloma patients. This includes employment by age and gender (before the onset of the

disease), sickness absence due to the disease, return to work after treatment, as well as work impairment because of the disease in those who are active in the labor market.

Based on our literature research, there is no evidence available on the distribution of multiple myeloma patients over industry sectors. Therefore, we assumed that the distribution equals the average population distribution by age and gender based on official numbers by the Federal Statistical Office [21].

When quantifying the productivity gains in paid work as a result of extended PFS, we had to consider that patients with multiple myeloma are generally less active in the labor market compared to healthy people due to the severity of the disease – irrespective of the length of PFS after treatment. Patients with hematological malignancies in general are among those at greatest risk of higher sickness absence, unemployment, and work-related disability in comparison to patients with solid tumors. And among those with hematological malignancies, multiple myeloma patients are those with the lowest return to work rate [22]. Employment rates before the onset of disease were taken from official statistics of the German Federal Statistics office and assumed to be equal to the population employment rates in the respective age group [23], [24]. Furthermore, we assumed that out of those who were employed at the beginning of the treatment, 80% enter long-term sick leave, while up to 39% of these gradually return to work during the first three years after the beginning of the treatment [22], [25].

Returnees to the labor market were still assumed to be subject to a certain degree of work impairment due to their disease. Based on evidence from quality of life questionnaire by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) [26], [27], general work and activity impairment in multiple myeloma patients was derived. We assigned a percentage reduction in work productivity to all patients depending on the stage of their disease.[4]

Labor productivity is defined as the ratio between output in terms of gross value added (production minus intermediate consumption) and employment in the respective industry sectors. We thus value economic contributions in

[4] Limitations in working or household jobs are measured in the EORTC QLQ-C30 by the item “role function”, which is based on the following two questions: “Are you limited in any way in doing either your work or doing household jobs?”; “Are you completely unable to work at a job or to do household jobs?”.

terms of gross value added (GVA), the most well-known and widely used measure of economic growth of nations and industries.

3.1.2 Indirect and induced effects

In addition to the direct productivity effects, we also considered interdependencies within the economy. Every productive activity within an economy is associated with consumption of goods and services from intermediate suppliers. As a result, further activities and creation of gross value added (indirect and induced effects) take place.

Direct GVA effects results from increases in the productivity of labor input and therefore correspond to the production-GVA-ratio of the respective sector. Indirect GVA effects, in turn, refer to increases in GVA creation in sectors that supply goods or services to the sector where a direct effect is observed. Induced GVA effects originate in increases in consumption as a result of direct and indirect effects.

By applying Leontief multipliers following the literature on input-output analyses, we quantify these indirect as well as induced gross value-added effects [28], [29].

3.1.3 Unpaid work

As stated above, one important aspect of the socio-economic footprint is the explicit consideration of the effects of better health on productive activities outside of the labor market. Innovative therapies restore the ability to perform both paid and unpaid work (e.g. housework, informal care or voluntary work). Thus, considering both is crucial in order to capture the welfare maximizing contribution of unpaid work within a society.

We followed the third person criterion and defined unpaid work as productive activities that could also be performed by another person [30]. Based on information from time use surveys on the amount of time that people spend on unpaid work activities, we applied the replacement cost approach and measure the value of the output produced by an equivalent market service [31], [32]. Productivity is thus valued according to the gross value added generated in the production of a market substitute, for example, by a worker employed in childcare or gastronomy [33].

3.1.4 Value of life

Focusing only on productivity effects when assigning a value to health or health improvements, disregards the immense value that health *per se* has for most humans. It is uncontroversial that the value of life goes far beyond the economic value that a person can contribute to a nation's economy in terms of productivity. Therefore, in addition to the economic value added from paid and unpaid work, we also incorporated the intrinsic value of life as one specific value dimension into the social impact. In an extensive literature review, Schlander et al. (2017) summarize research on the value of a statistical life year (VSLY). They include studies based on the *revealed preferences approach* as well as on the *stated preference approach* (both contingent valuation and discrete choice experiments). While their estimates show some heterogeneity by method and by region, the median European VSLY was estimated EUR 158,448 [34]. We drew on this number to assign a monetary value to the overall survival gains induced by using lenalidomide in the treatment of multiple myeloma.

Table II lists all input parameters for the calculation of the socio-economic footprint.

Table II: Main input parameter for the calculation of the socio-economic footprint

Variable	Values			Reference
Employment rates	**Age group**	**[male]**	**[female]**	[23], [24]
	20-29	73.1%	69.5%	
	30-39	89.1%	77.3%	
	40-49	90.3%	81.8%	
	50-59	84.8%	76.8%	
	60-69	39.9%	30.5%	
	70-79	7.9%	3.7%	
	80+	0%	0%	
Return to work rate	7 % (after 6 months) 19 % (after 1 year) 30 % (after 2 years) 39 % (after 3 years)			[22], [25]
Share of patients with early retirement / sick leave	80%			[22], [25]
Work impairment	23.4%			[26], [27]
Hours spent on unpaid work activities	According to time use survey (by gender and age group)			[31]
GVA per labor input	According to GVA per industry sector & per capita			[21]
Value of a statistical life year	EUR 158,000			[34]

3.2 Results

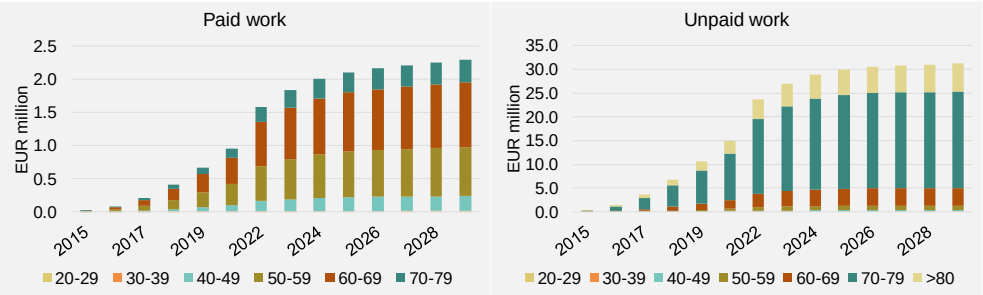
3.2.1 Main results

In the following, we present the direct productivity effects for both paid and unpaid work over the years from the introduction of lenalidomide for the respective therapy up to 2030 (end of year 2029). Results are presented separately for each therapy line.

Figure V depicts results for the first line therapy. From 2015 up to the year 2030, an additional 7,661 progression free life years can be saved. These correspond to productivity gains of EUR 20.1 m from paid work. In line with the assumption that patients above the age of 80 are no longer active in the labor market, these gains are attributable only to patients up to the age of 79. On average, every patient contributes about EUR 2,600 per progression free life year. Note that this number represents the average over all patients, including also those who are not active in the labor market (given the age distribution of MM patients, this is most patients in our model). Also note that this number refers to average GVA per capita (rather than average income, which constitutes a part of GVA alongside revenues, taxes/subsidies, and consumption of fixed capital).

7,661 progression free life years furthermore correspond to EUR 290.1 m in value added due to unpaid work. On average, every patient contributes EUR 37,800 per progression free life year. Value added contribution is considerably higher for unpaid work since we assume that all patients, irrespective of their employment status, perform unpaid work according to their age group and health status.

Figure V: Productivity gains in first line therapy (L1)

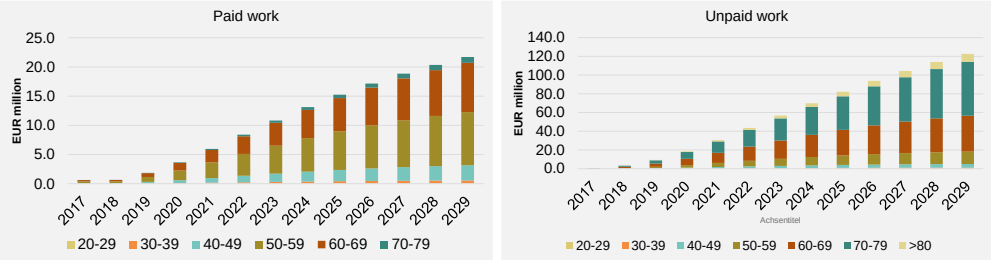


Authorization of lenalidomide for the maintenance therapy was in 2017. From 2017 up to 2030, 17,660 progression free life years can be saved. These correspond to value added gains of EUR 138.5 m from paid work. Here, on average, every patient contributes about EUR 7,800 per progression free life year. The reason for this number being considerably higher than in the first

line therapy, lies in the age distribution of the patients being treated in the respective therapy. As stated above, maintenance therapy with lenalidomide is applied after an autologous stem cell transplantation, which is indicated only for younger patients. These younger patients, in turn, are comparatively more active on the labor market, thus contributing more in terms of productivity gains from paid work.

With respect to unpaid work, a total of EUR 749.2 m in value added due to unpaid work will be gained up to the year 2030. On average, every patient contributes EUR 42,400 per life year. Again, the difference in the average numbers per person are attributable to the different age structure of the respective patient population.

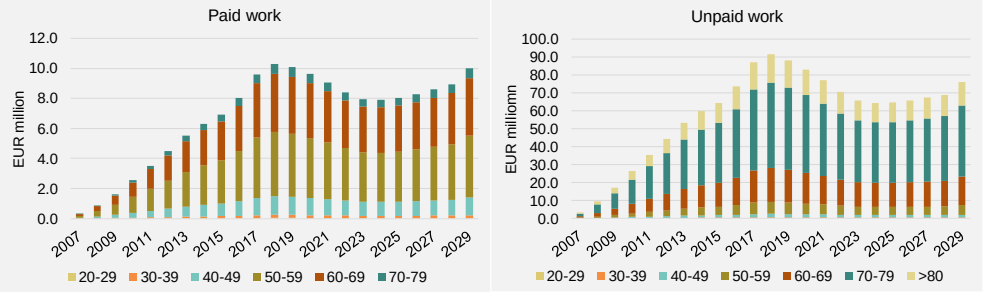
Figure VI: Productivity gains in maintenance therapy



For the later line treatments (L2+), we sum up the gains from 2007, when lenalidomide was first authorized, up to 2030. During this time span, a total of 38,745 progression free life years could and can be saved for patients in second line treatment. These correspond to value added gains of about EUR 156.9 m from paid work. On average, every patient contributes about EUR 4.050 per progression free life year.

Furthermore, about EUR 1,354.6 m in productivity due to unpaid work will be gained. On average, every patient contributes EUR 34.9 thousand in value added per progression free life year.

Figure VII: Productivity gains in further line therapies (L2+)



To sum up, through 2030, about 64,066.39 additional progression free life years can be gained by using Revlimid® and its generics respectively. This additional time is used either for work (paid) or for household production and voluntary work (unpaid work). Thus, the gained progression free life years

correspond to about 8.1m hours of paid work (5,952 years of paid work) in the multiple myeloma patient population and to about 79.8 m hours of unpaid work.

Based on these additional progression free life years, economic contributions in terms of additional GDP (based on paid work) sum up to EUR 315.5 m. Furthermore, additional value added from unpaid work sums up to about EUR 2,393 m.

Table III: Direct value added effects from paid and unpaid work in per therapy line

	L1 (no ASCT)	ASCT & Maintenance	L2+	Summe
PFS patient years	7,661.25	17,659.84	38,745.16	**64,066.39**
Value added* (paid work)	20,058.15	138,272.46	156,952.24	**315,484.85**
Value added*, per person	2.61	7.84	4.05	**4.92 (Ø)**
Value added* (unpaid work)	290,091.54	749,196.66	1,354,631.97	**2,393,920.16**
Value added*, per person	37.86	42.4	34.96	**37.36 (Ø)**

* In thousand EUR.

3.2.2 Stakeholder analysis

With the stakeholder analysis, we illustrate the effects that the additional productivity has for different stakeholders within the economy. Depending on the health effects of the medical innovation, these institutional effects can be interpreted as benefits either for the patients themselves, for employers, or for fiscal authorities (additional tax revenues): With higher productivity due to increased work capacity, all three institutions benefit from increased gross value added.

Patients themselves benefit from better health, increased quality of life and the ability to perform both paid and unpaid work activities. Additional or higher income, in turn, results in higher tax revenues for the fiscal authorities as well as additional contributions to social insurance agencies. This is because income taxes and social security contributions are deducted from employees' wages.

Employers in the public and private sector benefit from increased productivity of their employees as this raises production and gross value added.

[Wider economic effects (indirect and induced effects)] Direct gross value added of market based and non-market based economic activity creates additional indirect and induced effects for the German economy. Intermediate consumption and spending of additional income lead to gross value added for the economy as a whole in the amount of EUR 2,768.9 m

[Employers] A share of about 26.8 % of gross value added results in (gross) profits for employers. Employers benefit from direct gross value added sums up to EUR 84.5 m.

[Patients / Private households] Another share of about 30.0 % of gross value added results in (net) wages for the workers. In sum, patients themselves (employees) benefit from about EUR 94.6 m of wages. Furthermore, patients benefit from additional active time and the unpaid activities that they can perform. In sum, these are worth EUR 2,393.9 m for the patients

[Institutional effects] Based on their gross wages, employees must pay wage taxes and social security contributions (these amount to about 7.91 % and 18.0 % of gross value added, respectively).In sum, based on additional direct gross value added, about EUR 81.7 m are paid to fiscal authorities and social security institutions.

4 Value-invest analysis

With the value-invest analysis, we compared the social impact with the additional costs that occur due to the treatment of MM patients with lenalidomide. On the one hand, we considered additional direct treatment costs (costs for lenalidomide) and indirect treatment costs (costs for other medications used in lenalidomide-based combination therapies) in all three treatment scenarios. On the other hand, we also considered general average health care costs that occur due to a longer lifetime – independent of actual MM treatment costs. We did not include possible cost savings resulting from less frequent hospitalizations or other changes in treatment paths other than follow-up medical treatments since information on these aspects cannot be derived from the results of the clinical trials. This may lead to an eventual overestimation of costs (due to underestimation of possible cost offsets).

4.1 Treatment costs

Treatment costs include all medication costs, including additional services (e.g. secondary treatments) that are associated with each treatment regimen. Until the expiration of the patent for lenalidomide, all patients treated with lenalidomide will receive Revlimid®. From 2025 onwards, Revlimid® will be partly replaced by generics in all treatment regimens. This assumption regarding the time of patent expiration is in line with information in the 2016 annual report of Celgene. Table IV lists our assumptions regarding the gradual replacement of Revlimid® by generics and the according price reduction.

Table IV: Share of generics and price reduction over time

Years after patent expiration	Share of generics in %	Price reduction in %
1 year	45.42 %	52.0 %
2 years	81.3 %	54.0 %
> 2 years	95.0 %	70.5 %

Source: [35], [36].

In the following tables (Tables V-VII), we list average costs that occur for the treatment with each regimen per patient and per treatment cycle. Costs refer to the recommended treatment schedules as defined by the pharmaceutical

manufacturer. Differences in costs depending on the treatment cycle result from different treatment schedules at the beginning and at later stages during the therapy (e.g. a more intense dosing in the first cycles and a less intense dosing in the remaining cycles), as well as differing accompanying medications.

4.1.1 First line therapy (L1)

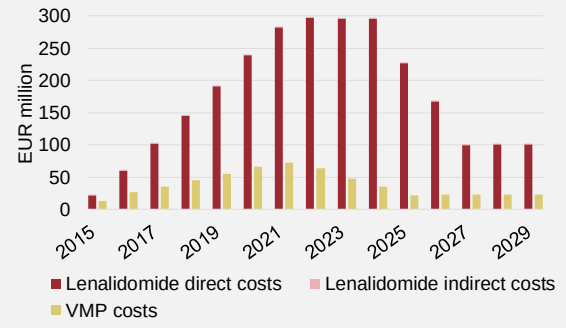
Table V: Treatment costs per cycle (L1 therapy)

Treatment	Cycle	Cost per cycle (€)
Rd	1-4	7,544.85
	5-progression	7,468.68
VMP	1-6	5,599.72
	7-14	2,752.56

Source: [37]–[39].

Figure VIII depicts the aggregate treatment costs for both scenarios over time. It differentiates between costs that are directly attributable to lenalidomide alone and those that are attributable to other medications (indirect costs). From 2015 up to 2030, the *difference* in treatment costs for MM patients between lenalidomide and VMP sums up to EUR 2.1billion. About 95% of additional costs are attributable to costs for lenalidomide. As can be seen in the graph, there is a significant reduction in treatment costs after the expiration of the patent of lenalidomide.

Figure VIII: Accumulated treatment costs for first line therapy (L1 therapy, no ASTC)



4.1.2 Maintenance therapy

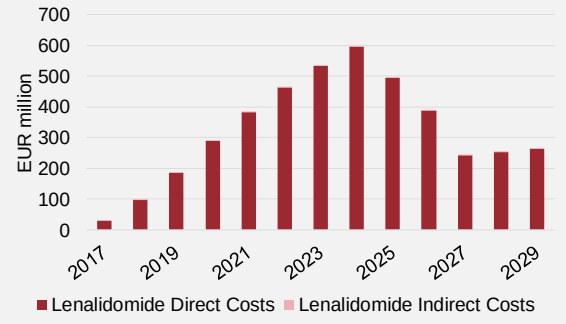
Table VI: Treatment costs per cycle (maintenance therapy)

Treatment	Cycle	Cost per cycle (€)
R mono	1-2	8,623.20
	3-progression	8,620.19
Placebo	*No medication*	

Source: [37]–[39].

Since “no treatment” (placebo) does not induce costs, Figure IX displays costs for the maintenance treatment only with lenalidomide. From 2017 up to 2030, the *additional* treatment costs for MM patients sum up to EUR 4.3billion. About 99% of additional costs are attributable to costs for lenalidomide. Also here, aggregate treatment costs decrease significantly after patent expiration.

Figure IX: Accumulated treatment costs for maintenance therapy



4.1.3 Later line therapies (L2+)

Table VII lists treatment costs for the different lenalidomide-based treatment options (including triplet therapies) in later line therapies. It becomes apparent that costs for a treatment with the novel triplet therapies exceed the costs for a simpler doublet therapy considerably. Treatment costs with HD Dexa, however, lie clearly below any therapy with lenalidomide.

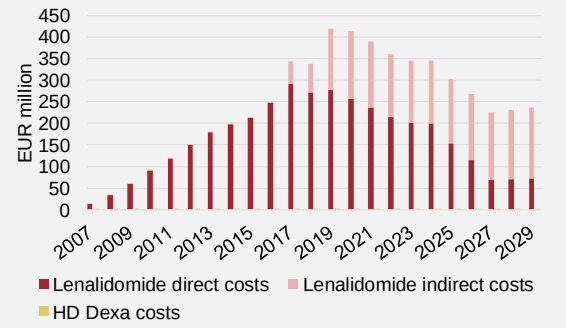
Table VII: Treatment costs per cycle (L2+ therapies)

Treatment	Cycle	Cost per cycle (€)
Rd	1-2	7,542.05
	3-4	7,540.82
	5-progression	7,492.30
DRd	1-2	39,540.47
	3-6	23,509.70
	7-progression	15,494.94
Krd	1	13,900.90
	2	14,671.82
	3-12	14,668.44
	13-progression	12,282.12
EloRd	1-2	22,057,83
	3-progression	13,015.77
IxaRd	1-2	16,929.58
	3-progression	16,929.20
HD Dexa	1-2	81.30
	3-progression	32.78

Source: [37]–[39].

From 2007 to 2030, the *difference* in treatment costs for MM patients between lenalidomide regimens and HD dexa sums up to EUR 6.4 billion.

Figure X: Accumulated treatment costs for further line therapy (L2+)



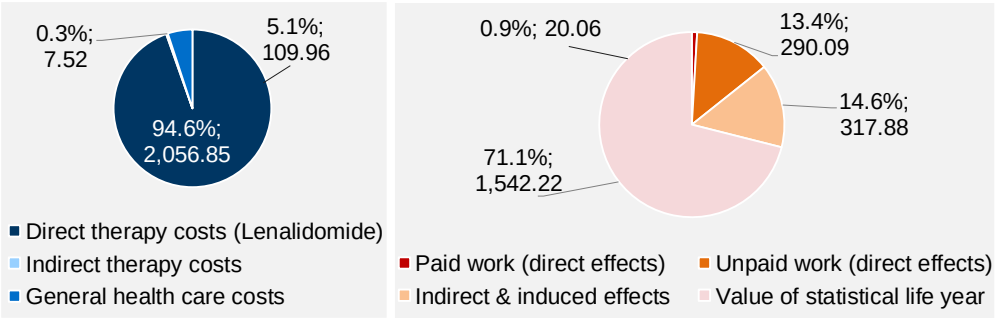
4.2 Comparing impact and costs

Comparing aggregate additional treatment costs with the social impact reveals very different cost-benefit ratios depending on the treatment line. Aggregate additional treatment costs comprise therapy costs attributable to lenalidomide (direct therapy costs), therapy costs attributable to other medications, including other components of the triplet therapies, as well as additional general health care costs that arise because of longer survival.

4.2.1 First line therapy (L1)

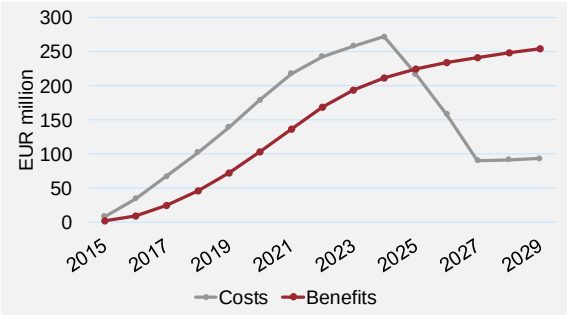
Additional costs for a treatment with Rd in the first line therapy sum up to EUR 2,174 million. As can be seen in Figure XI, about 95% of these costs are attributable to the treatment costs with lenalidomide. The social impact for the first line therapy, in turn, sums up to around EUR 2,170 million. As can be seen in the right-hand panel of Figure XI, around 71% of this value is attributable to the intrinsic value of additional lifetime, monetarized in the value of a statistical life year. The remaining 29% of this value are attributable to productivity gains, including direct, indirect and induced value added gains.

Figure XI: Composition of aggregate additional costs and social impact in first line (L1) therapy



The analysis of aggregate costs and the social impact over time (see Figure XII) reveals that, while additional costs exceed the benefits until 2024, once the patent expires, additional treatment costs fall significantly and remain clearly below the benefits. Considering the time period 2015 to 2030, the value-invest ratio, i.e. the ratio between benefits and costs, is 0.99. Benefits and costs therefore almost balance out.

Figure XII: Social impact and additional costs from 2015 to 2030 (L1 therapy)

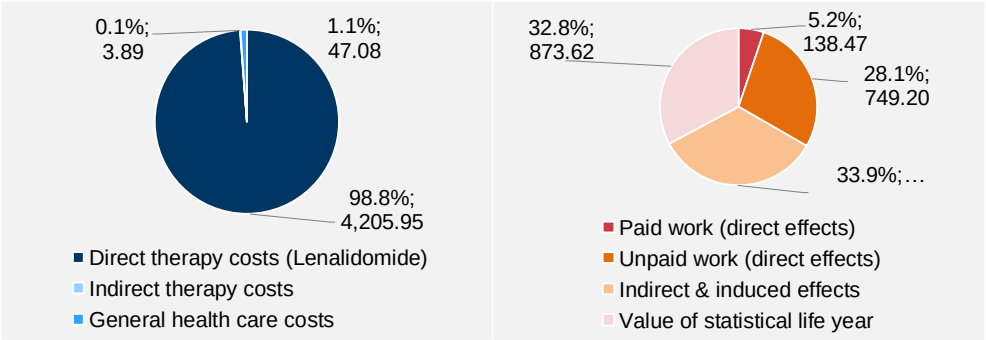


4.2.2 Maintenance therapy

For the maintenance treatment, additional costs for the treatment with lenalidomide (R mono treatment) sum up to EUR 4,257 million. Again, a large share of the costs is attributable to direct treatment costs. Only about 1% of additional treatment costs can be attributed to indirect treatment costs and additional general health care costs as a consequence of longer survival. The social impact sums up to EUR 2,665 million, resulting in an overall value-invest ratio of 0.63.

Compared to the first line therapy, the share of the value of life in the total social impact is relatively lower (around 33%). This can be explained by the higher share of relatively young and active patients in the patient population eligible for ASCT and therefore for a maintenance treatment with lenalidomide. Also, as is apparent in Figure XIII, incremental gains in OS, which are the basis for the quantification of the value of life years, are considerably lower than the gains in PFS for maintenance therapy.

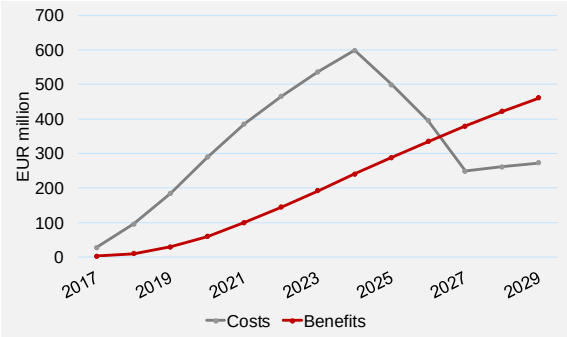
Figure XIII: Composition of aggregate additional costs and social impact in maintenance therapy



For maintenance therapy, too, costs will decrease significantly after patent expiration from 2025 onwards. While additional costs clearly exceed benefits in the first years after drug approval for maintenance therapy, according to our

forecasts, this relation will be reversed from 2027 onwards when aggregate benefits will be higher than aggregate additional costs (see Figure XIV).

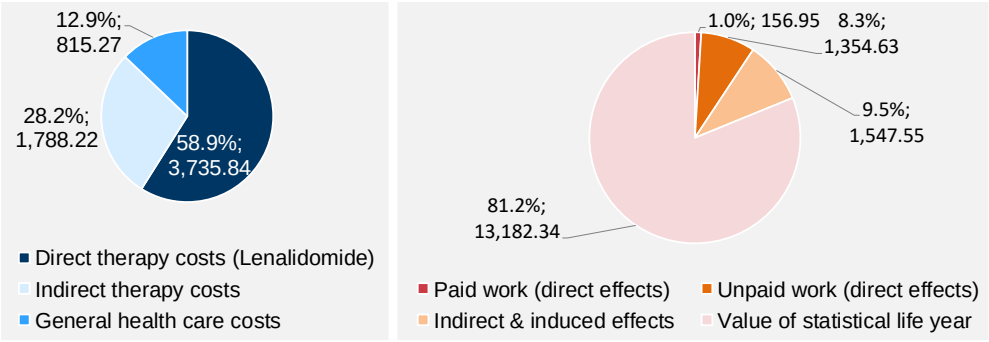
Figure XIV: Social impact and additional costs from 2017 to 2030 (maintenance therapy)



4.2.3 Later line therapies (L2+)

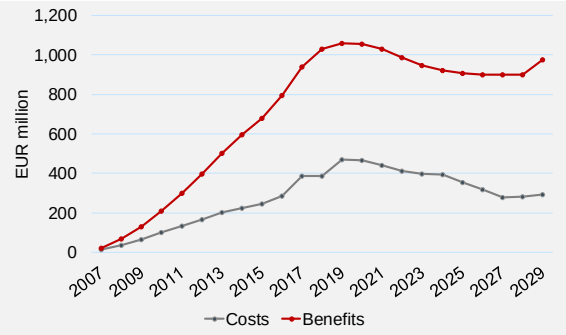
Additional therapy costs for later line therapies amount to EUR 6,339 million over the time period 2007 to 2030. Figure XV shows that, contrary to L1 and maintenance therapies, directs costs that are attributable to lenalidomide account only for about 59% of all additional costs. Since all four triplet therapies that are available from 2015/2016 onwards, are considerably more expensive, these indirect medication costs also account for around 28 %. Another 13 % are attributable to additional general health costs.

Figure XV: Composition of aggregate additional costs and social impact in L2+ therapies



The social impact of using lenalidomide-based medication in L2+ therapy lines amounts to EUR 16,241 million. This high additional benefit is mainly attributable to the huge gap in efficiency between HD Dexa and all treatment options including lenalidomide. Comparing the social impact with the additional costs reveals a value-invest ratio of 2.56. This high ratio is also reflected in Figure XVI, which shows the social impact and additional treatment costs over time. During the whole period from 2007 to 2030, the social impact exceeds the additional costs.

Figure XVI: Social impact and additional costs from 2007 to 2030 (L2+ therapies)



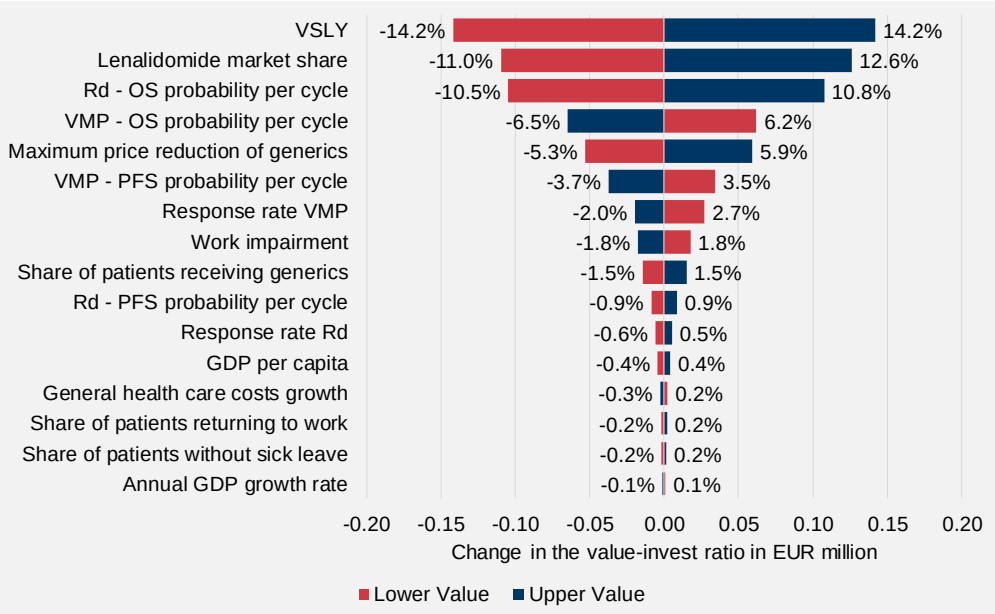
5 Sensitivity Analysis

Most input parameters in our model are based on assumptions or derived from statistical estimations (e.g. transition probabilities in the Markov model), both of which are subject to uncertainty. This applies especially to those assumptions regarding future developments. We therefore conducted a deterministic one-way sensitivity analysis in order to assess changes in model outputs upon changing input parameters. To this end, each input parameter was varied by a specific amount and effects on model outputs, i.e. socio-economic benefits and costs, are reported. As is usual for a one-way sensitivity analysis, each parameter was varied separately. While this does not allow for the analysis of the combined effect of uncertainty in all parameters, it is a straightforward and easy way to assess the relationship between each model input parameter and the outputs. It indicates how sensitive the model is to changes in input parameters and at the same time it permits identifying those input parameters that have the strongest impact on model results.

One challenge in deterministic sensitivity analysis is to choose plausible upper and lower bounds for the variation of input parameters. For response rates and PFS/OS probabilities derived from fitted Kaplan Meyer curves from clinical trials, we applied 95% confidence limits of the estimated parameters as upper and lower values. For most parameters derived from the literature and for input parameters based on administrative statistics, we applied a range of variability of +/- 20% or of a defined absolute value if this seemed reasonable based on plausibility considerations. Tables IX to XI in the Appendix list all parameters that were varied in the sensitivity analysis and their range of variability (upper and lower bounds).

Figure XVII depicts the change in the value-invest ratio of the L1 therapy if each of the listed input parameters is varied according to the range of variability as defined in Table IX.

Figure XVII: Sensitivity of the value invest ratio (L1 therapy)



Each bar represents the change in the value-invest ratio if the input parameter listed on the left-hand side is changed to its upper or lower bound value. As is apparent from the diagram, the value-invest ratio for the L1 therapy is most sensitive to the assumed value of a statistical life year (VSLY) as well as to lenalidomide market shares. An increase in the VSLY of about 20% to EUR 189,000 leads to an increase in the value-invest ratio of 0.14 points or 14.2%. Increase in the lenalidomide market share of 20% over the years 2015 to 2029 leads to an increase in the value-invest ratio of about 0.126 points or 12.6%. Generally, the value-invest ratio exhibits a relatively high sensitivity to parameters from clinical studies and a relatively low sensitivity to assumptions on GDP and labor market assumptions.

The baseline result for the value-invest ratio in first line therapy is 0.99 - i.e. additional costs almost equal the social impact. Changing input parameters can thus shift the value-invest ratio to either above 1 or further below 1. This means that whether the social impact exceeds the cost or vice-versa critically depends on the underlying assumptions.

Figure XVIII and XIX report results of the sensitivity analysis for the maintenance and later line (L2+) therapies, respectively. Also, regarding these therapy lines, there is a relatively high sensitivity to changes in parameters from clinical studies and changes in assumptions regarding the pharmaceutical market. In contrast, sensitivity to GDP and labor market assumptions is relatively low.

Figure XVIII: Sensitivity of the value invest ratio (maintenance therapy)

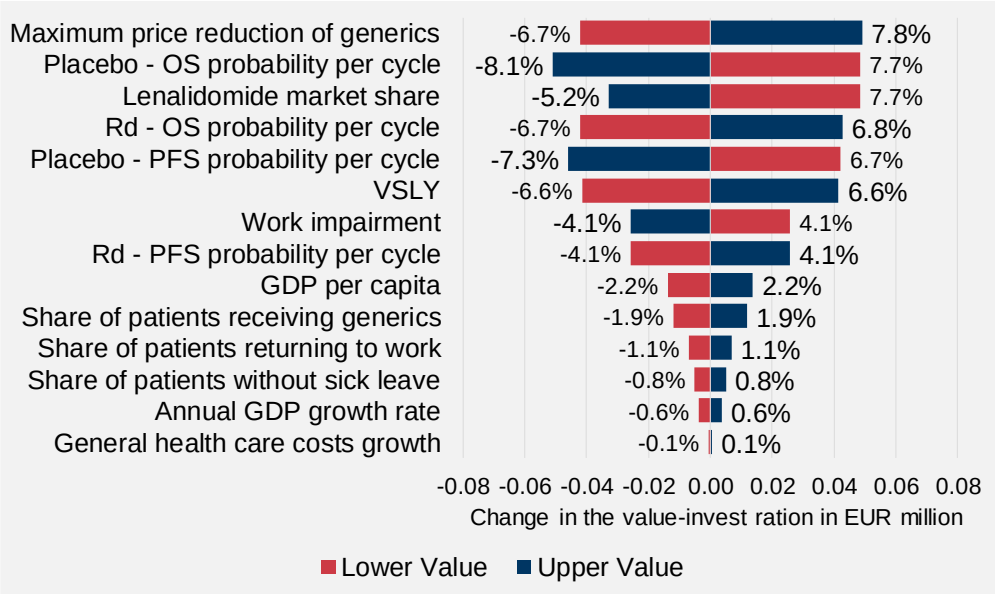
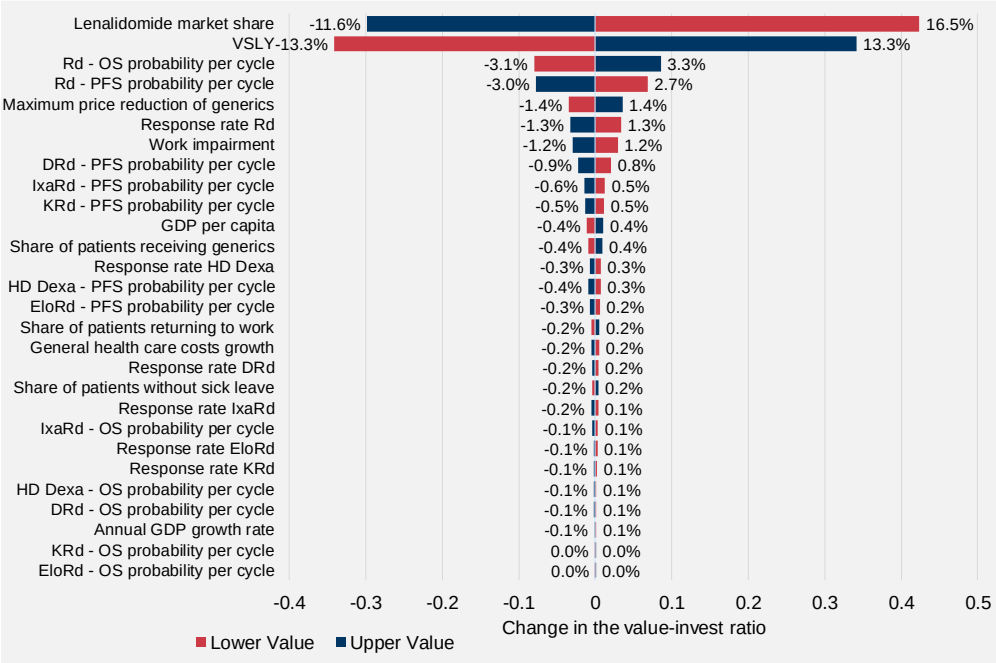


Figure XIX: Sensitivity of the value invest ratio (L2+ therapies)



6 Discussion and conclusion

6.1 Summary of results

In this study, we quantified the impact of an innovative drug in oncology field. We considered both the health benefits and socio-economic benefits that are associated with using lenalidomide in the treatment of multiple myeloma.

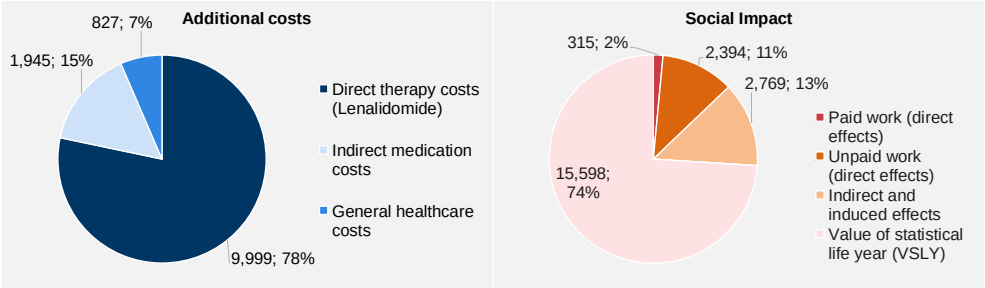
By including productivity effects generated by unpaid work we challenged a common argument against the consideration of productivity in assessing the value of medical innovation. It states that these should not be included since they only apply to patients active in the labor market. By including the productivity effects generated by unpaid work, we extended the reach of productive time being monetized to include the patients beyond the retirement age.

We showed that, over the time period 2007 to 2030, the use of lenalidomide in all therapy scenarios, for which its use is approved, generates 64,066 additional progression-free life years compared to alternative (best available) treatment options. Additional overall life years amount to 98,723. Assuming an intrinsic value of this lifetime according to the average value of a statistical life year, this health benefit corresponds to EUR 15,508 million.

Further, considering productivity effects that result from this improved health, the use of lenalidomide has the potential to generate around EUR 315 million in value added (GVA) from paid work and additional EUR 2,394 million in value added from unpaid work. Indirect and induced GVA effects further amount to EUR 2,769 million. Considering all treatment lines over 2007 to 2030, the overall social impact sums up to EUR 21,076 million.

Additional costs for the treatment of MM patients with lenalidomide-based regimens amounts to EUR 12,771 m. Comparing the overall social impact with additional treatment costs yields a value-invest ratio of 1.65. Figure XX depicts the social impact and the costs by impact and cost category.

Figure XX: Overall costs and social impact (L1, maintenance, and L2+)



6.2 Limitations

This study faces several limitations regarding both the health and the socio-economic footprint.

In simulating progression-free and overall survival over time, we had to rely on survival rates (depicted in Kaplan Meyer curves) generated in clinical trials. These Kaplan Meyer curves, however, only cover a defined period of observation, i.e. the period over which the clinical trial was conducted. Therefore, in extrapolating survival beyond this time period, assumptions on constant survival had to be made. This may not equal real average long-term survival of MM patients, but depicts an approximation derived from best available evidence.

Regarding both health effects and costs, it is important to note that these do not necessarily reflect the actual care situation in Germany as they rely on the circumstances of clinical trials and on an additional set of assumptions. Clinical trials generally represent an optimal setting for treatment. For example, adherence and persistence of treatment typically differ in a real-world setting, affecting both drug effectiveness as well as therapy costs. However, the treatment of serious illnesses demands tight treatment schedules, deviations should therefore typically be small. Further, in case of deviations, these would apply to either therapy scenario, be it a lenalidomide-based or the comparator treatment. Therefore, we argue that it is valid to extrapolate the clinical trial conditions when calculating incremental benefits and costs.

Also, health benefits quantified in this study are limited to those that are measured in the course of the clinical trial. Possible differences between treatment options regarding quality of life or other relevant health-related outcomes are not considered due to missing information on significant effects of lenalidomide-based treatments on these outcomes based on clinical trials.

Further, our assumptions on constant comparator treatments over the whole time period considered in our model may be questioned. Over the last 15 years, there have occurred substantial improvements in the therapy of MM

and further improvements can be expected to occur in coming years. Thus, realistic comparator treatments against which innovations are measured against when determining incremental health benefits will differ over time. At the time of writing this report (May 2020), further therapy options had already been approved, making the definition of the best alternative therapy somewhat obsolete. Still, comparing a lenalidomide-based treatment to the best alternative treatment option available at an earlier time, serves the purpose of this study; that is: Providing an exemplary quantification of the societal and economic benefits of a medical innovation.

It must nevertheless be noted that the benefits presented in this study should be interpreted as an economic potential rather than a simulation of actual developments that can be expected to happen as a result of the introduction of an innovative drug. Labor market dynamics are generally influenced by factors that go beyond the supply of (healthy) workers. Possible indirect productivity effects such as spill-over effects or compensation mechanisms within companies are not considered. Also, we do not take into account possible effects on healthcare providers' productivity that may be induced by changes in the demand for healthcare services.

A further important aspect not considered in this study are effects of improved health on patients' family members and/or informal care givers. In addition to patients themselves, also caregivers are often exposed to stress and reduced quality of life. Besides, many informal caregivers reduce their employment in order to provide care to a relative, which in turn impacts overall productivity and generation of value added in the economy. These indirect effects constitute an important aspect from an economic point of view and should receive further attention in research.

Generally, in any case of uncertainty regarding specific assumptions or input parameters, we adopted the most conservative assumption, i.e. the assumptions that resulted in the smallest incremental benefit of the lenalidomide-based treatment. In Chapter 5 we show that variations in input parameters of up to +/- 20% have in mostly moderate effects on our overall results.

6.3 Conclusion

Despite the listed limitations, this study provides a valuable contribution to the discussion about the value of medical innovations. Focusing on the treatment of MM patients with lenalidomide (both Revlimid® and its generics), the study shows that there are important societal and economic benefits in addition to the direct health benefits that result from an effective treatment. Not only

patients themselves, but also the economy as well as public households' benefit from increased population health.

While we do not consider *all* value dimensions that are currently being discussed in the scientific literature, we incorporate important dimensions that go beyond a mere clinical advantage. Our results show that, depending on the dimensions considered, conclusions regarding the value-invest ratio of "investments in health" such as through an innovative therapy may well differ. In general, the societal impact of medical innovations, as assessed within this study, represents a useful tool in the current debate on value-based pricing and on the dimensions that should be taken into account when applying this approach.

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Annex

Table VIII: Number of patients entering each therapy line and share of patients receiving lenalidomide based treatment (per year)

	L1		Maintenance		L2+	
	Patients	% receivinglenalidomide-treatment	Patients	% receivinglenalidomide-treatment	Patients	% receivinglenalidomide-treatment
2007					3,140	13%
2008					3,640	20%
2009					3,948	26%
2010					4,147	36%
2011					4,303	38%
2012					4,514	47%
2013					4,672	49%
2014					4,730	50%
2015	3,935	16%			4,920	50%
2016	3,987	23%			5,096	66%
2017	4,034	30%	851	57%	5,175	64%
2018	4,071	36%	1,364	64%	5,201	47%
2019	4,060	45%	1,664	67%	5,165	43%
2020	4,007	53%	2,035	70%	4,961	38%
2021	4,037	56%	2,194	60%	4,645	34%
2022	4,068	44%	2,314	60%	4,529	30%
2023	4,103	44%	2,333	60%	4,785	30%
2024	4,137	44%	2,353	60%	4,987	30%
2025	4,165	44%	2,369	60%	5,146	30%
2026	4,198	44%	2,387	60%	5,301	30%
2027	4,235	44%	2,408	60%	5,471	30%
2028	4,271	44%	2,429	60%	5,593	30%
2029	4,312	44%	2,452	60%	5,678	30%

Source: [8], [10], Celgene internal information.

Table IX: Variation of parameters – Sensitivity analysis of L1 therapy

Parameter	Baseline Value	Lower bound	Upper bound	Type of variation
Rd - Response rate	0.75	0.708	0.794	95% CI
VMP - Response rate	0.71	0.684	0.728	95% CI
Rd – PFS probability per cycle	0.977	0.975	0.978	95% CI

VMP – PFS probability per cycle	0.979	0.977	0.981	95% CI
Rd – OS probability per cycle	0.990	0.989	0.991	95% CI
VMP – OS probability per cycle	0.994	0.993	0.995	95% CI
Lenalidomide market share (over 2015-2030)		*Different values*		+/- 20%
GDP per capita		*Different values*		+/- 20%
Annual GDP growth	1.5 %	1.0 %	2.0 %	+/- 0.5 pp.
Share of patients without sick leave	20.0 %	216.0 %	24.0 %	+/- 20%
Share of patients returning to work	25 %	20.0 %	30.0 %	+/- 20%
Work impairment	23.4 %	18.72 %	28.08 %	+/- 20%
Value of statistical life year	158,000 €	126,400 €	189,000 €	+/- 20%
General health care costs growth	1.5 %	1.0 %	2.0 %	+/- 0.5 pp.
Max. price reduction of Revlimid generics	70.05 %	56.4 %	84.6 %	+/- 20%
Share of patients receiving generics (max.)	95.0 %	90.0 %	100.0 %	+/- 5.0 pp.

Table X: Variation of parameters – Sensitivity analysis of maintenance therapy

Parameter	**Baseline Value**	**Lower bound**	**Upper bound**	**Type of variation**
R mono – PFS probability per cycle	0.988	0.987	0.989	95% CI
Placebo – PFS probability per cycle	0.976	0.974	0.978	95% CI
R mono – OS probability per cycle	0.995	0.994	0.995	95% CI
Placebo – OS probability per cycle	0.993	0.992	0.994	95% CI
Lenalidomide market share (over 2015-2030)		*Different values*		+/- 20%
GDP per capita		*Different values*		+/- 20%
Annual GDP growth	1.5 %	1.0 %	2.0 %	+/- 0.5 pp.
Share of patients without sick leave	20.0 %	216.0 %	24.0 %	+/- 20%
Share of patients returning to work	25 %	20.0 %	30.0 %	+/- 20%
Work impairment	23.4 %	18.72 %	28.08 %	+/- 20%
Value of statistical life year	158,000 €	126,400 €	189,000 €	+/- 20%
General health care costs growth	1.5 %	1.0 %	2.0 %	+/- 0.5 pp.
Max. price reduction of Revlimid generics	70.05 %	56.4 %	84.6 %	+/- 20%
Share of patients receiving generics (max.)	95.0 %	90.0 %	100.0 %	+/- 5.0 pp.

Table XI: Variation of parameters – Sensitivity analysis of L2+ therapies

Parameter	Baseline Value	Lower bound	Upper bound	Type of variation
Rd – Response rate	0.646	0.676	0.616	95% CI
DRd – Response rate	0.929	0.937	0.921	95% CI
KRd – Response rate	0.871	0.882	0.860	95% CI
EloRd – Response rate	0.785	0.804	0.767	95% CI
IxaRd – Response rate	0.783	0.801	0.766	95% CI
HD Dexa – Response rate	0.275	0.302	0.247	95% CI
Rd – PFS probability per cycle	0.955	0.961	0.950	95% CI
DRd – PFS probability per cycle	0.985	0.987	0.983	95% CI
KRd – PFS probability per cycle	0.950	0.954	0.945	95% CI
EloRd – PFS probability per cycle	0.965	0.969	0.961	95% CI
IxaRd – PFS probability per cycle	0.968	0.971	0.965	95% CI
HD Dexa – PFS probability per cycle	0.861	0.878	0.845	95% CI
Rd – OS probability per cycle	0.989	0.990	0.988	95% CI
DRd – OS probability per cycle	0.993	0.993	0.992	95% CI
KRd – OS probability per cycle	0.988	0.989	0.987	95% CI
EloRd – OS probability per cycle	0.988	0.989	0.986	95% CI
IxaRd – OS probability per cycle	0.911	0.991	0.990	95% CI
HD Dexa – OS probability per cycle	0.973	0.976	0.970	95% CI
Lenalidomide market share (over 2015-2030)		*Different values*		+/- 20%
GDP per capita		*Different values*		+/- 20%
Annual GDP growth	1.5%	1.0%	2.0%	+/- 0.5 pp.
Share of patients without sick leave	20.0%	16.0%	24.0%	+/- 20%
Share of patients returning to work	25%	20.0%	30.0%	+/- 20%
Work impairment	23.4%	18.72%	28.08%	+/- 20%
Value of statistical life year	158,000 €	126,400 €	189,000 €	+/- 20%
General health care costs growth	1.5%	1.0%	2.0%	+/- 0.5 pp.
Max. price reduction of Revlimid generics	70.05%	56.4%	84.6%	+/- 20%
Share of patients receiving generics (max.)	95.0%	90.0%	100.0%	+/- 5.0 pp.

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