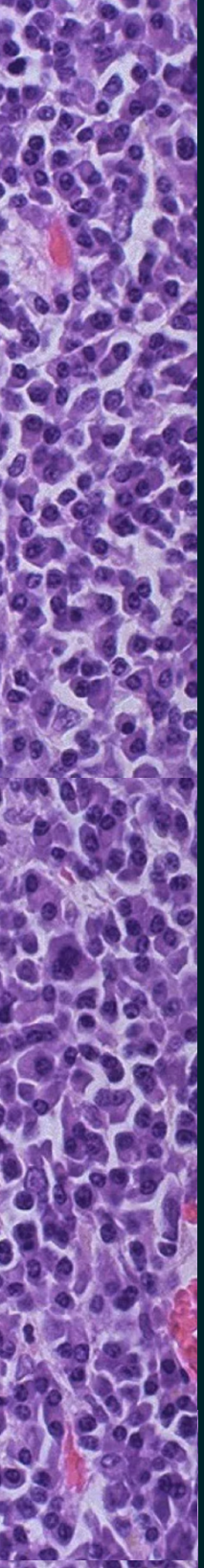

Cost-Effectiveness of First-line Daratumumab for Multiple Myeloma in a Dutch Setting

MSc Thesis Health Economics, Policy & Law

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Cover image: Hematoxylin and eosin stain of bone marrow in a multiple myeloma patient (40x).[1]

Multiple myeloma is defined as "≥10% clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytoma with one or more CRAB criteria and at least one biomarker of malignancy".[2]

In this image, the bone marrow biopsy is literally *"chock-full of plasma cells"*.[1]

Preface

Exactly one year ago I was doing my rotations in neurology, psychiatry and geriatrics, just a few months before I was to start studying in Rotterdam. Definitely did I recognize the relevance of health economics in the hospital. I was regularly faced with the economic consequences of modern-day (Western) medicine. Apparently stable psychiatric patients were sometimes hospitalized for weeks; as an unexperienced intern fulfilling one of his learning goals – *verwonderen* – I scented inefficiency. When I asked the psychiatric resident "why?", he told me it was necessary to titrate drug concentration. Healthcare costs are strongly skewed towards the final year of life.[3] I saw it happening: terminal patients that for some reason were referred to the geriatrics department, demanding a lot of diagnostics.

Physicians not always seemed to be fully aware of the amounts of money they were spending. Is that wrong in itself? We ought to feel blessed that, apparently, the Dutch system does not immediately collapse, even if physicians do not bother so much about costs. But, healthcare expenditures keep rising, so when will *all* physicians eventually have been made cost-conscious? *Doelmatigheid in de zorg* has recently been introduced as a key topic in residential training,[4] but elementary medical school lags behind in my view. Inspired by Health Economics, Policy & Law, three peer students and I therefore decided to introduce a multidisciplinary approach to healthcare (covering health economics, governance & soft skills, and technological innovation) at Utrecht University by creating our own elective course.[5]

There might also be a downside to placing more emphasis on the € sign in medical education. Health technology assessments (HTAs) definitely are pivotal to inform reimbursement decision makers. At the same time, while writing this thesis, the physician-to-be in me sometimes had his reservations. Have I spoken to a single myeloma patient during the thesis trajectory? Have I been able to get a picture of what it is like living with multiple myeloma, apart from some searching on patient forums? Estimating informal care use was but one item to which this is relevant. Ctrl F "assum" reveals 48 hits. Lots of assumptions and clinical uncertainty; self-evidently there is a role for physicians here. Hans van Delden, professor of medical ethics, recently recalled the items that should be part of a HTA in his lecture on 'Technical innovation & society' in our student-driven course: clinical effects, yes. Bare euros, yes. But also, societal impact and ethical consequences, amongst others, should be integrally part of HTAs.

Over the past year I have become more cost-conscious. I undoubtedly consider the knowledge I have acquired in health economics, and HTA in particular, of great value. However, I have to make sure, especially during the first weeks back in the clinic, by no means to let it interfere with quality of care.

Summary

Background Recently, the ALCYONE trial has demonstrated that progression-free survival (PFS) can be improved if daratumumab (D) is added to the induction scheme consisting of melphalan, prednisone and bortezomib (MPV) in multiple myeloma (MM) patients over 70 years. Although this scheme comes with an unprecedented improvement in PFS, costs concerned with the treatment of MM are expected to increase simultaneously. Currently, in the Netherlands daratumumab is only reimbursed as monotherapy in refractory MM. It is pivotal to assess the cost-effectiveness of the new MPVD treatment scheme, in order to inform decision making with respect to reimbursement of first-line daratumumab.

Methods A four-state partitioned survival model was developed to calculate whether MPVD is cost-effective compared to MPV by means of a cost-utility analysis. Costs and effects were calculated from a Dutch societal perspective over a lifetime horizon, with effects being expressed in quality-adjusted life years (QALYs). Based on all costs and effects, a base case incremental cost-effectiveness ratio (ICER) was calculated. To assess sensitivity of this ICER to alternative scenarios and variation in parameter input, deterministic (DSA) and probabilistic sensitivity analyses (PSA) were performed, respectively. ICERs were compared to the societal willingness-to-pay threshold (WTPT) of €80,000 per QALY gained. A value-of-information (VOI) analysis was performed to explore the maximum amount society should be willing to pay for additional research to reduce decision uncertainty. This is expressed as the population expected value of perfect information (PEVPI).

Results Estimated mean survival in the MPVD arm was 5.75 QALYs, as compared to 5.16 QALYs in the MPV arm. Total costs amounted to €1,477,394 and €1,241,478, respectively. Drug-related costs amounted to €688,454 in the MPVD arm, and €366,357 in the MPV arm. The base case ICER was €400,906 per QALY gained. DSAs showed that the base case ICER is robust, yet particularly sensitive to variation in health state utilities and the price of daratumumab. The PSA yielded a probabilistic ICER of €418,928 per QALY gained (11% of simulations below usual WTPT) and showed that MPVD is not cost-effective with 89% certainty at the usual WTPT. The PEVPI amounted to €6,635,543 for a number of 176 patients annually affected by the decision over an effective decision life time of 5 years.

Conclusions The MPVD scheme is not cost-effective at the usual Dutch WTP threshold. Based on this, it is recommended not to reimburse daratumumab within the first-line MPV scheme. Especially extrapolated survival was associated with a large degree of uncertainty. Improved maturity of survival data is essential to decrease uncertainty. Additional data on survival and consequent treatment schemes are currently being collected. Results from the present analysis should be revisited as soon as these data have been made available and shifts in treatment practices for advanced myeloma have acted out.

Samenvatting

Achtergrond De ALCYONE-studie heeft recentelijk laten zien dat progressievrije overleving (PVO) verbeterd kan worden door toevoeging van daratumumab (D) aan het inductieschema met melfalan, prednison en bortezomib (MPV) in multipel myeloom (MM) patiënten boven de 70. Alhoewel dit schema ongekende PVO-winst oplevert, leidt het waarschijnlijk ook tot forse toename van behandelkosten voor MM. In Nederland wordt momenteel alleen daratumumab-monotherapie vergoed bij refractair MM. Het is belangrijk om de kosteneffectiviteit van het MPVD-schema te beoordelen, zodat een geïnformeerde keuze gemaakt kan worden om eerstelijns daratumumab al dan niet te vergoeden.

Methoden Middels een kosten-utiliteitsanalyse werd berekend aan de hand van een gepartitioneerd overlevingsmodel met vier toestanden of MPVD kosteneffectief is vergeleken met MPV. Kosten en effecten werden berekend vanuit een Nederlands maatschappelijk perspectief over een levenslange tijdhorizon, waarbij effecten werden uitgedrukt in *quality-adjusted life years* (QALYs). Op basis van alle kosten en effecten werd de basale incrementele kosten-effectiviteitsratio (ICER) berekend. Om de gevoeligheid voor alternatieve scenario's en variatie in parameterinvoer te testen, werden respectievelijk deterministische (DSA) en probabilistische sensitiviteitsanalyses (PSA) uitgevoerd. ICER's werden vergeleken met de Nederlandse standaard (referentiewaarde, w_{ref}) van € 80.000 per gewonnen QALY. Middels een *value-of-information* (VOI) analyse werd geïnventariseerd welk bedrag, uitgedrukt als de populatie *expected value of perfect information* (PEVPI-waarde) maximaal besteed zou moeten worden aan verder onderzoek om de onzekerheid rondom de beslissing tot al dan niet vergoeden te reduceren.

Resultaten De geschatte gemiddelde overleving in de MPVD-arm was 5,75 QALY's, tegenover 5,16 in de MPV-arm. Totale kosten waren respectievelijk € 1.477.394 en € 1.241.478. Medicijn-gerelateerde kosten kwamen uit op € 688.454 in de MPVD- en € 366.357 in de MPV-arm. De basale ICER was gelijk aan € 400.906 per gewonnen QALY. DSA's toonden aan dat de ICER robuust is, maar vooral gevoelig is voor variatie in utiliteiten en de prijs van daratumumab. De PSA leverde een ICER op van € 418.928 per gewonnen QALY (11% van de simulaties viel onder de w_{ref}) en liet zien dat MPVD met 89% zekerheid niet kosteneffectief is naar Nederlandse maatstaven. Voor 176 patiënten die jaarlijks getroffen worden door de beslissing en over een periode van vijf jaar, was de PEVPI gelijk aan € 6.635.543.

Conclusies Het MPVD-schema is niet kosteneffectief naar Nederlandse maatstaven. Daarom is het advies om daratumumab niet te vergoeden gecombineerd met eerstelijns MPV. Vooral geëxtrapoleerde overleving was geassocieerd met een hoge mate van onzekerheid. Overlevingsdata over een langere opvolgperiode zijn essentieel om deze onzekerheid te reduceren. Data hierover en over vervolgschema's worden momenteel verzameld. De resultaten van deze analyse moeten herzien worden zodra deze data beschikbaar zijn en verschuivingen in het behandellandschap hun uitwerking hebben gehad.

Contents

Introduction

Multiple myeloma treatment

Multiple myeloma (MM) is a neoplastic disorder of plasma cells, affecting 0.8 per 10,000 people in the Netherlands annually.[6] The pallet of treatment options for MM has been largely extended over the past years by new strategies through the addition of immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies to existing chemotherapeutic plus steroidal regimens.[7] Various novel agents, including bortezomib (Velcade®, a proteasome inhibitor), lenalidomide (Revlimid®, an immuno-moderator), and daratumumab (Darzalex®, a CD-38 antibody), have attracted attention for their unprecedented effect on progression-free (PFS) and overall survival (OS).[8] Costs of MM treatment are, parallel to the growing number of treatment possibilities, also increasing. Total treatment costs reached $15,000 on average per patient per month in 2014 in the United States.[9] In the Netherlands, costs of refractory or relapsed MM (demanding second-, third- or fourth-line treatment) amounted to €3,981 (SD €3,538) per patient per month on average in 2009.[10]

What treatment scheme is chosen for MM patients mainly depends on the eligibility for autologous stem cell transplantation (ASCT). ASCT is the preferred treatment in all patients under the age of 70 years, according to the Dutch HOVON (Dutch Foundation for Adult Haemato-Oncology) treatment guideline.[11] In case patients are ineligible for ASCT, mostly because of older age (>70 years; approximately half of all new MM patients in the Netherlands, see Fig. 1),[6] there are several criteria that determine which of the various schemes is best.[11] For patients ineligible for ASCT at diagnosis (except for patients treated in the phase II HOVON 143 clinical trial testing efficacy and tolerability of ixazomib, daratumumab and dexamethasone in frail patients), the Dutch treatment guideline advises first-line induction therapy with a scheme of either melphalan, prednisone and bortezomib (MPV), or lenalidomide and dexamethasone (Rd).[11] Kidney function, presence of neuropathy, high risk classification defined as del(17p), t(4;14), and/or t(14;16) mutations, preferred treatment duration and drug administration route determine whether MPV or Rd prevails.[11]

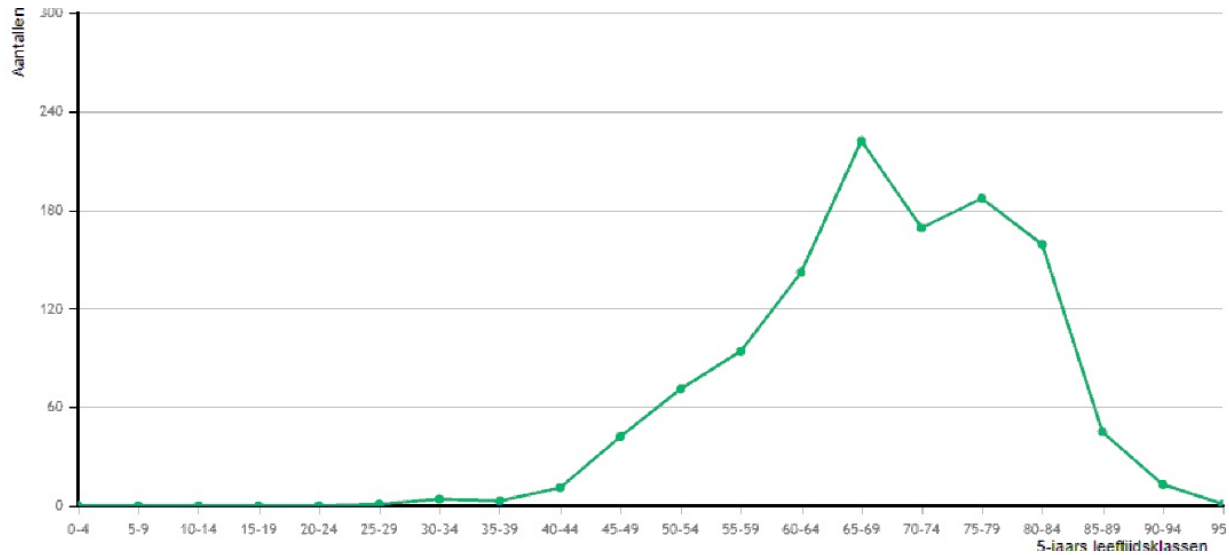
The ALCYONE trial: daratumumab added to first-line treatment

A recent randomized controlled trial, the ALCYONE trial, has demonstrated a beneficial effect on survival (especially PFS) of adding daratumumab to the MPV induction scheme followed by daratumumab maintenance treatment in patients ineligible for ASCT.[12] In the older MM population ineligible for ASCT, the MPV scheme could thus be improved. While clinical results are favorable, this new treatment is expected to increase treatment costs for MM patients. Health-related quality of life (HR-QoL) data concerned with the use of these agents need yet to be analyzed in the follow-up phase of this study.[12] While reimbursement of daratumumab (and if reimbursed, under what circumstances) is

a topic of debate among Dutch policy makers,[13] cost-effectiveness analyses from a Dutch healthcare perspective are currently lacking for first-line application of daratumumab. Budget impact estimations and pharmacoeconomic evaluations focused on second-line application concluded that daratumumab is unaffordable for this indication (see the section on theoretical background).[13] However, with other novel agents in the pipeline, and price negotiations ongoing, it is highly relevant to investigate the cost-effectiveness of first-line application of daratumumab in addition to the MPV scheme for MM patients ineligible for ASCT in a Dutch setting. The results of this thesis help further facilitate the reimbursement discussion that is expected to take place amidst a variety of yet to be invented, expensive agents.[13]

The objective of this thesis is to calculate for the ASCT-ineligible population at diagnosis whether MPV alone or MPV plus daratumumab is favorable in terms of cost-effectiveness. This is calculated for the Dutch healthcare setting by means of a cost-utility analysis (CUA). The study population is particularly relevant for its share to total MM incidence: approximately half of all people newly diagnosed with MM in the Netherlands in 2016 were aged over 70 (Fig. 1), and therefore ineligible for ASCT.

Fig. 1: Incidence of multiple myeloma in the Netherlands in 2016 by age.[6]



Theoretical background

Daratumumab in Dutch (future) context

Janssen-Cilag International Ltd. was granted an orphan designation for its CD38 monoclonal antibody daratumumab (Darzalex®) in July 2013 by the European Medicines Agency.[14] Cost-effectiveness analyses and budget impact estimations for the application of daratumumab after at least one prior line of treatment have been included in the 'package advice daratumumab', i.e. the reimbursement dossier by the Dutch Health Institute to support the Minister of Health in making a decision on reimbursement of daratumumab.[13] The cost-effectiveness analysis of adding daratumumab to the Rd scheme for relapsed disease demonstrated a wide range of uncertainty around the incremental cost-effectiveness ratio (ICER): €129,721 to €338,087 per QALY gained.[13] The analysis of daratumumab addition to the combination of bortezomib and dexamethasone (Vd) in the same setting yielded a lower ICER of €56,830 to €109,742 per QALY gained.[13] Because of the high expected costs of daratumumab and forthcoming fear of crowding-out other healthcare demands at population level, this drug has not yet been included in the basic benefit package.[15] Unless ongoing price negotiations result in a lower price for daratumumab, it will not be included in the basic benefit package either.[13] Daratumumab has been placed in the so-called 'drug lock' (*pakketsluis*), where it is only reimbursed as monotherapy in refractory MM.[15] The Dutch Health Institute will inform the Minister of Health in 2020 again on the clinical and, importantly, economic outcomes of daratumumab.[13]

Set against this thesis, an important question to ask, is what the composition of consequent treatment schemes would be in case the MPVD scheme became the preferred first-line treatment regimen. The above cost-effectiveness analyses were conducted with clinical data from the CASTOR (Vd[D])[16] and POLLUX (Rd[D])[17] trials, which studied daratumumab application in patients that underwent at least one prior line of treatment. These populations were rather heterogeneous, with for instance >60% of subjects who had undergone ASCT prior to daratumumab. CASTOR and POLLUX data is the only available data regarding second-line application of daratumumab in combination schemes, yet it cannot be used for the MM population at stake in this thesis. One could argue that the current preferred second-line scheme of Rd + carfilzomib (KRd) after a first-line bortezomib-containing regimen could be replaced by a daratumumab-containing variant with time, especially since HOVON is already pointing at daratumumab as a potential successor of carfilzomib in its guideline.[11] Also, Dutch hematologists believe that there may be an important role for daratumumab in advanced myeloma, given their estimations of daratumumab use included in prior budget impact analyses.[13] It would be too presumptive, however, to already assume daratumumab use in a second-line regimen in this thesis.

Whether there is clinical rationale whatsoever for persistent treatment with daratumumab in consequent lines, even if patients develop progression during first-line daratumumab-containing regimens, is unknown. It is, however, a pivotal point to address, since upcoming assumptions regarding consequent treatment schemes are largely dependent on this. On the one hand, hematologists do not expect daratumumab to be used if it was already administered in prior lines against which the patient developed resistance, given their utilization estimations in the 'packet advice daratumumab'.[13] On the other hand, daratumumab acts through multiple mechanisms, and the extent to which CD38 is expressed on the cell membrane has been identified as a predictor for response to daratumumab.[18] CD38 expression in myeloma cells can be stimulated by all-trans retinoic acid, potentially even in non-responders.[19] This might make daratumumab-resistant patients respond again. Still, the highly experimental nature of the aforementioned allows to assume, for now, that daratumumab is not used again in consequent treatment lines after progression on daratumumab in the MPVD arm. With respect to second-line treatment, in case of progression directly after bortezomib, the Dutch treatment guideline advices a two- or three-drug lenalidomide-based regimen.[11] Three-drug regimens definitely come with a relevant improvement in PFS compared to two-drug variants,[20] and should be considered as first choice, especially if patients experience clinically relevant symptomatic disease.[11] Since this thesis will not deal with treatment responses and patient characteristics at an individual and detailed level, it is assumed that second-line treatment always consists of the three-drug scheme lenalidomide (Revlimid®), dexamethasone and carfilzomib (Kyprolis®), abbreviated 'KRd'.

Models for economic evaluations

Economic evaluations can be conducted using either a model (or simulation), or as part of a randomized controlled trial. Given time and budget constraints, and for practical reasons, it was decided to develop a model in this master's thesis. First, existing models for MM that have been described in literature were reviewed. As a starting point for a scoping review on the alternatives for cost-effectiveness models, a review article published in 2015 was used.[21] This article yielded one relevant article in which a Markov model for MM treatments was described. To identify more recent literature, the search strategy underlying the review article was repeated in PubMed/MEDLINE for the time interval February 2013 until 26 January 2018 (Appendix A1). The entire scoping search yielded three model alternatives (Markov model, individual simulation approach, and a partitioned survival model). For the Markov model, four-[22] and seven-state[23] models have been described. Furthermore, individual simulation approaches with three or four disease states have been used, with which the influence of individual (disease) characteristics on transition probabilities can be taken into account.[24–26] Lastly, a number of partitioned survival models with, again, three[27,28] or four[22] disease states were retrieved through the search.

Within a Markov model, transition probabilities are often fixed, at least for a number of cycles. In partitioned survival models, however, the number of patients occupying health states is predicted using the area under the curve of parametric survival distributions for PFS and OS.[29] Since individual patient characteristics will be less relevant to this analysis, and the analysis is performed based on RCT data on OS and PFS for the treatment schemes of interest, a partitioned survival model is most appropriate.

Methods

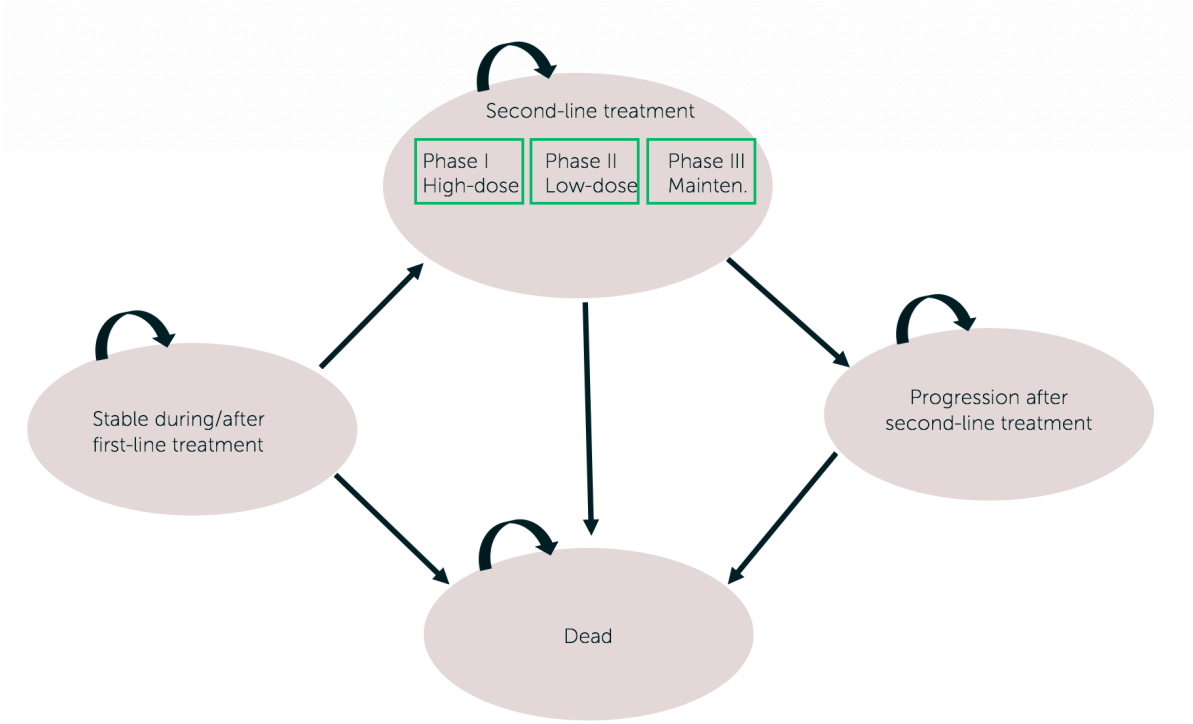
Description of the partitioned survival model

The cost-effectiveness of the MPVD scheme was compared to MPV by means of a cost-utility analysis (CUA) from a Dutch societal perspective and in accordance with the recommendations for economic evaluations in healthcare.[30] Hence, effects were expressed in quality-adjusted life years (QALYs), for which time being alive was weighted for utilities attached to being alive. Utilities can range from 0 and 1, where 1 indicates 'perfect health' and 0 indicates 'dead'. Effects were discounted at 1.5% annually, costs at 4.0%, in line with the Dutch guideline.[31] Since this thesis aims at investigating the cost-effectiveness of combination schemes with expensive drugs as first-line treatment, it is important that treatment lines in which cost-saving effects may be achieved through earlier introduction of daratumumab are properly reflected in the model. Especially in advanced lines of therapy, a large pallet of schemes is at hand, and each patient demands a tailored approach.[11] It was hypothesized that, if daratumumab applied in first-line therapy would be cost-effective at all, such would be partly achieved by postponement of more expensive, tailored treatment in late stages of MM. Cost discounting can lead to reduced net life-time treatment costs, after all.

A life-time horizon, half-cycle corrected partitioned survival model modified from the model structure by Garrison *et al*.[23] (Fig. 2) was devised using Microsoft® Excel (Microsoft® Office for Mac, version 16.11.1). For simplification, treatment responses (e.g., 'very good partial response') were not distinguished, and it was assumed that 'progression after first-line treatment' and 'PFS during/after second-line treatment' could be combined as one state. The latter implies that all patients with progression were assumed to immediately start consequent treatment. The ALCYONE investigators are still collecting follow-up data on progression-free survival after consequent therapies in patients enrolled in the daratumumab trial.[12] As these data are not available yet, it was impossible to divide progression after first-line treatment from second-line treatment. The number of people in 'stable disease' and 'dead' followed from the Kaplan Meier curves in the ALCYONE trial.[12] The remaining people were divided over progression after first-line and progression after second-line treatment. Progression-free survival in the KRd second-line treatment scheme derived from the ASPIRE trial[32] was used to calculate the number of patients in 'progression during/after second-line treatment'.[33] It demands emphasis that the ASPIRE trial lacks the external validity to apply results one-to-one to the MM population over 70 years and ineligible for ASCT. However, ASPIRE data currently is the only data available on the KRd regimen. Treatment recommendations for patients over 70 years are also based on this trial, which is considered very strong evidence (graded as SORT A level of evidence) by HOVON.[11] As soon as follow-up ALCYONE data on consequent treatment will have been published, ASPIRE data in this

model should be immediately replaced with ACYONE data. Completion of the long-term follow-up of ALCYONE patients is scheduled for October 2021.[34]

Fig. 2: Four-state partitioned survival model devised for this analysis



'Mainten.' denotes maintenance therapy with Rd without carfilzomib

Extrapolation of survival curves

Extrapolation of ALCYONE trial data (first-line treatment)

Original Kaplan Meier curves from the ALCYONE publication were uploaded in WebPlotDigitizer version 4.1 (https://apps.automeris.io/wpd/) to retrieve X and Y coordinates from the Kaplan Meier curves semi-automatically. Using these coordinates and patient level data on the number of censors at given time moments, the numbers censored per three weeks were estimated according to the interpolation method described by Hoyle & Henley.[35] Data were then exported to *RStudio* (version 1.0.136 2009-2016) and fitted to distributions recommended by NICE in the DSU technical support document 14,[36] that were available in the R package *survival* (version 2.42-3.1):[37] Weibull, lognormal, loglogistic, and exponential. Consequently, the distribution fit for OS and PFS was assessed for all parametric distributions using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and clinical plausibility, including comments on the extrapolation of CASTOR and POLLUX data by the Delphi panel consulted for the 'package advice daratumumab'.[13] Weibull distributions for both OS and PFS yielded the lowest AIC (except for OS of the MPVD arm). Weibull distributions were also considered most appropriate from a clinical perspective; for almost 20 years plateau phase

characteristics have been respected as predictors of long-term survival.[38] The plateau phase is defined as the phase during which maximum treatment response is achieved.[38] Recently it was shown that longer time-to-plateau is associated with increased OS in a large cohort of 1099 Americans with newly diagnosed MM.[39] Since time-to-plateau demonstrates large variations among patients, it is not directly reflected in PFS and OS curves if still a relatively large proportion of patients is alive. However, based on Mellors *et al*.,[39] with time (vastly exceeding ALCYONE follow-up time) OS curves may flatten out, which is best reflected by Weibull distributions. For PFS, Weibull distributions best reflect the initial course of the Kaplan Meier curves, whereas other distributions largely overestimate PFS within follow-up time. A Weibull distribution was also most frequently recommended by the hematologists in the Delphi panel.[13]

BICs were not provided automatically by R, but could be calculated algebraically, since:

$$\begin{cases} AIC = 2k - 2\ln(\hat{L}) \\ BIC = \ln(n)\,k - 2\ln(\hat{L}) \end{cases}$$

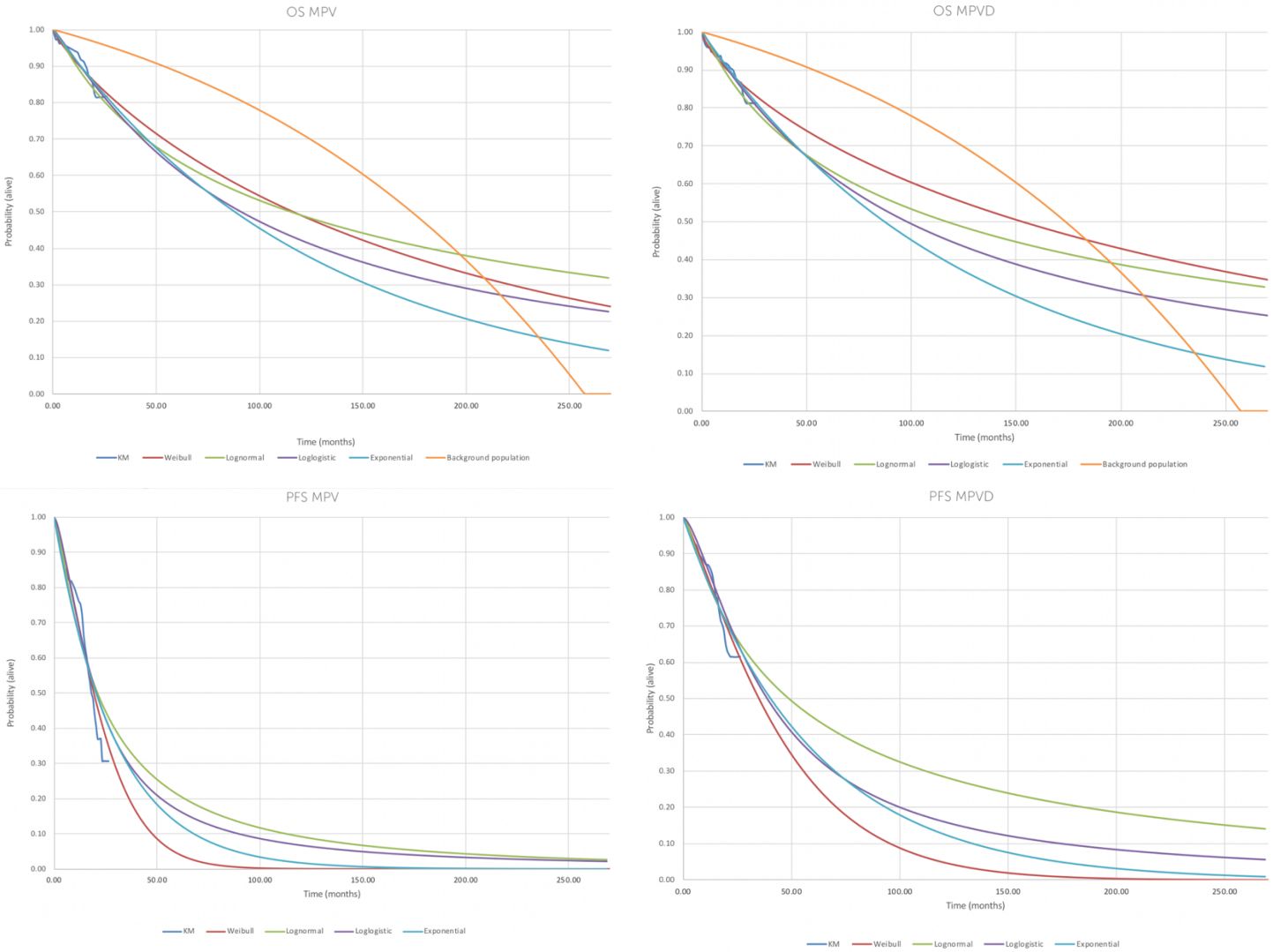
It follows that:

$$BIC = k \cdot (\ln(n) - 2) + AIC \qquad \text{(Equation 1)}$$

Where k denotes the number of parameters estimated by the model and n the number of data points on the original Kaplan Meier curve. BICs were lowest for those distributions that also yielded the lowest AICs, except for OS in the MPVD arm. Moreover, for PFS in the MPVD arm the $BIC_{exponential}$ was slightly lower than $BIC_{Weibull}$ (< 0.1%). Initial choices for distributions were maintained based on BIC values.

Deterministic sensitivity analyses demonstrating the effect of alternative parametric distributions will be presented in the results section. A Weibull distribution was most frequently recommended by the hematologists in the Delphi panel. Because Weibull distributions assume proportional hazard, log-cumulative hazard plots were constructed to test for this assumption (Appendix A2). Although the proportional hazard assumption was not met for OS, alternative distributions reflected the most likely clinical scenario even worse. In PFS, other distributions largely overestimated survival, and were inferior to Weibull distributions, therefore. Original Kaplan Meier curves for OS and PFS are displayed along with their corresponding parametric distributions in Fig. 3 (enlarged versions are in Appendix A3).

Fig. 3: Original Kaplan Meier curves and corresponding parametric distributions



Development of second-line treatment state using ASPIRE trial data

Data on PFS in the KRd arm of the ASPIRE trial was digitalized and parameterized in the same way as described above for the ALCYONE data. Here as well, a Weibull distribution demonstrated the best fit, both clinically and statistically. Since patients continuously are at risk of progression after first-line treatment, new patients will start second-line therapy in each cycle. For a number of reasons, it was necessary to keep second-line patients in the "cohort" in which they originally started second-line therapy: firstly, the hazard function is time-dependent, hence the proportion of patients progressing towards third-line therapy changes with time. Secondly, the KRd regimen consists of three phases (KRd with high-dose K, KRd with low-dose K, and Rd maintenance therapy without K). Not only does composition and dosing of drugs in the KRd regimen differ between the three phases; it also affects resource use. Finally, the rate and consequent costs of adverse events in second-line treatment can only be calculated if all new patients entering second-line treatment are kept in a distinct cohort. Imaginably,

this necessitated construction of an $m \times n$ matrix, where m equals the number of cycles, and n denotes the cycle number at which a cohort of patients starts second-line therapy. In this way, the second-line treatment trajectory could be considered a tunnel state, which, however, could be exited at any cycle. For every cohort 1, 2, …n the number of patients entering second-line treatment was multiplied with the parametric distribution that was fitted to ASPIRE data. Patients that progressed on first-line treatment, and therefore started second-line therapy, were estimated using the following equations:

$$N_{progressed\ on\ firstline\ treatment} = 1000 - death - PFS \quad \text{(Equation 2)}$$

$$N_{newly\ progressed} = \begin{cases} \Delta N_{progressed\ on\ firstline\ treatment} & if\ > 0 \\ \left|\Delta N_{stable\ firstline\ treatment}\right| & otherwise \end{cases} \quad \text{(Equation 3)}$$

Thus, the n^{th} cohort of patients starting second-line therapy entered the n^{th} tunnel. Patients could only exit 'their' tunnel if they either progressed towards third-line therapy, or if they died. For every cycle, the number of patients stable during second-line therapy was calculated based on the total number of patients in all second-line treatment tunnels together. Finally, it was then possible to estimate the number of patients in third- and fourth-line therapy together:

$$N_{third\ and\ fourth\ line} = min\left\{(1000 - PFS - death - stable_{second-line}), OS\right\} \quad \text{(Equation 4)}$$

Correction for life expectancy of the general population

As can be observed from the extrapolated survival curves, regardless their disease, a proportion of MM patients will reach a 'normal' life span, perfectly in line with empirical findings.[40] At some point in time, survival is therefore bound to life expectancy of the general population. To correct for this, a power term was fitted ($R^2 = 0.9997$) to life table data for the Dutch general population (sample year 2015) from the World Health Organization[41] using MATLAB (Appendix A4):

$$p(alive|age) = -2.248 \cdot 10^{-14} \cdot age^{6.942} + 0.9961 \quad \text{(Equation 5)}$$

This function predicted the number of people alive in a same-sized, same-aged, background cohort. From the cycle where the (extrapolated) survival probability of the study population exceeded that of the general population onwards, the latter was used for OS. Distributions of patients in the MPVD and MPV arm (cohort size in both arms equals 1,000) over all four health states, including three distinct second-line treatment phases, are displayed in Appendix A5.

Variables

Utilities

Utility values for MM patients have been reported for several populations (e.g., American, Northern-European) and different disease states. Even in case geographical and cultural population and disease severity are equal, reported utilities vary to a large extent, depending on – amongst others – the exact type of treatment, age, and patients' sense of disease improvement.[42] The consequent tangle of utility values reported in literature, each time focused to a very specific (non-Dutch) MM population, renders distillation of utility values for older Dutch MM patients from literature a difficult undertaking. A free literature search was performed on 2 February 2018 in PubMed/MEDLINE (search strategy in Appendix A1). Based on this, utility values were estimated for the population of interest. Relative utility decrements rather than absolute utilities were compared across articles to establish estimations of utilities for the specific Dutch population. Daratumumab is known for its favorable adverse events profile,[12] which logically suggests application of an alternative utility value for patients in the daratumumab arm. This was addressed by calculating utility decrements for adverse events, which occur less often under daratumumab treatment. Utility decrements were calculated for all grade 3 and 4 adverse events and corrected for duration of the adverse event. It was assumed that grade 1 and 2 adverse events are of such mild nature, that QoL burden of these adverse events is implicitly included in base-case utilities.

Resource use and costs

The societal perspective applied in this analysis dictates that all costs related to the disease had to be taken into account. A top-down micro-costing approach was applied wherever it was feasible.[31] Prices were converted to Dutch 2018-euros using consumer price indices (CPIs) of total goods and purchasing power parities (PPPs) published by the OECD.[43,44]

Resource use in first- and second-line treatment

The Dutch MM treatment guideline by HOVON does not provide any recommendations on frequency of monitoring (outpatient hematologist consultations) and evidence-based diagnostic work-up during or after myeloma treatment regimens.[11] All assumptions underlying calculations of resource use with respect to monitoring and follow-up/treatment response diagnostics can be found in Appendix C1. Assumptions were based on expert opinion from UpToDate and the UMC Utrecht myeloma treatment protocol.[45,46] A group of medical specialists was consulted as a Delphi panel for the pharmacoeconomic evaluation of daratumumab in advanced myeloma.[13] Expert opinion from this panel on administration mode during second-line treatment (outpatient, day-care, inpatient) was also applied to the first-line scheme in this analysis, since the ALCYONE trial, nor the Dutch guideline provide data on this.[11,12] However, administration costs in the same estimation were considered unrealistic, particularly since

cost specifications were lacking.[13] Data underlying these estimations were retrieved from an open-source database on all oncologic Dutch patients subjected to chemotherapeutic treatments (Open DIS data, Dutch Health Authority).[47] It should be questioned whether this population is representative for patients undergoing MPV(D) or KRd treatment. Therefore, only the fraction of patients that is administered their drugs inpatient was used from this source. Administration costs itself were based on data specific for hematology departments.[48]

An important innovation which potentially heavily affects the incremental cost-effectiveness ratio of daratumumab-containing regimens to other regimens, is home administration of bortezomib.[49,50] In the base-case analysis it was assumed that bortezomib is exclusively administered in the hospital (Appendix C1), but the effect of home administration was studied with a deterministic scenario analysis. For the health state reflecting stable disease during/after first-line treatment, average costs were adjusted to the phase of treatment, e.g., dosing frequency decrease in advanced phases of treatment. Although the Dutch treatment guideline advises dosage adjustment (e.g., melphalan, dexamethasone, bortezomib) in the elderly or comorbid patients, the ALCYONE trial suggests all participants are administered the same dose of medication. Moreover, some discrepancies between the study medication and Dutch guideline recommendations were present. These were handled according to assumptions 1-3 in Appendix C1.

Concomitant medication was in first instance based on medication administered in the ALCYONE trial, but was checked afterwards with the Dutch treatment guideline. Specific concomitant medication for the MPVD arm consisted of Tavegil and montelukast; acyclovir was administered in combination with the bortezomib-containing regimen.[11] Aspirin (or Ascal) is recommended in combination with lenalidomide-containing regimens,[11] and was administered accordingly. Dalteparin (or any other light molecular weight heparin) is recommended after a venous thromboembolic (VTE) complication, but given the low incidence (3%)[51] of VTE under lenalidomide (if also under VTE prophylaxis with Ascal or Aspirin), this was neglected. Dosages of intravenous and subcutaneous drugs were calculated per administration, corrected for vial sharing if this option was selected in the model. Cumulative dosages per treatment cycle were calculated for oral drugs, since pills can be broken in half or even in four. Zoledronic acid was administered once per four weeks (fixed) in line with the recommended dosage for the prevention of skeletal complications, along with daily Calci Chew (Calcium and vitamin D).[52]

Costs of adverse events were only taken into account for grade 3 and 4, except for some KRd-related adverse events; prevention of hypertensive complications is of great importance while under treatment with KRd.[11] Since hypertensive complications such as myocardial ischemia and acute renal failure always have significant financial consequences, even if grade 1 or 2 (think of the need for temporary dialysis, coronary angiography, percutaneous coronary interventions, etc.) all grades of hypertension,

cardiac failure, acute renal failure and ischemic heart disease were taken into account in the cost calculations.

Input values for resource use and costs will be presented in the results section.

Resource use in advanced stages (third- and fourth-line treatment)

Although it was shown that the range of resource use in advanced stages of MM is not *per se* wider than in earlier lines of treatment,[53] options for treatment regimens are numerous. HOVON advises non-academic hematologists to consult a HOVON expertise center after second- or third-line treatment, so even more advanced treatment can be planned while latest clinical evidence is respected to the highest possible level.[11] A group of Dutch hematologists was asked to make predictions on likely treatment regimens for advanced MM after Dutch market access of daratumumab.[13] These estimations departed from the assumption that daratumumab is only applied after at least one prior line of treatment (CASTOR and POLLUX trials). Nevertheless, these predictions were used to derive expert opinion on the treatment choices made in practice. For instance, it seemed from these predictions that hematologists do not consider reuse of daratumumab likely in patients that were already administered daratumumab in a previous line of treatment.[13] A micro-costing approach to estimate resource use costs in third- and fourth-line treatment is complicated because dosage is tailored to patient wishes and perceived disease burden.[11] Therefore, it is difficult to estimate amounts of drugs used from total drug cost data collected in another country than the Netherlands. Costs of advanced treatment are not provided in the cost-effectiveness models included in the 'package advice'.[13] As a starting point it was assumed that total drug costs for third-line treatment and beyond collected in France[54] could be used in this analysis (after correction for inflation and purchasing power). French list prices of most agents (except for lenalidomide) could not be retrieved from French formularies.[55–57] Even if list prices for all drugs had been available, prices may not reflect actual costs, since risk sharing agreements are often kept confidential, so that ex-factory list prices can be maintained in official documents. Another ESHPM MSc thesis, that has been written this academic year, deals with costs of all lines of myeloma treatment in the Netherlands.[58] (Average) drug costs of the treatment schemes used in the model were taken from this thesis and compared to French data to assess whether costs could be considered realistic. If French and Dutch costs were concordant, Dutch prices were taken as input values. Importantly, it was taken into account that France can to a higher extent negotiate (price-volume) discounts given its large market share, hence Dutch drug (list) prices may be higher, despite external price referencing *and* France being in the comparison basket of the Netherlands.

Indirect medical costs

Future medical costs were calculated with the PAID tool, version 1.1, of the Institute for Medical Technology Assessment (iMTA).[59] Based on median age in the ALCYONE trial, it was assumed that

all patients in the cohort are 71 years at diagnosis (so cycle 1 of the model). Diseases related to MM that were excluded from the future medical costs estimation are: non-Hodgkin's disease, other lymphoid cancer and leukemia, diseases of the blood and blood-forming organs (if patients developed these [malignant or benign] hematological conditions, these events were captured in the trial data); and osteoporosis (since all MM patients start preventive treatment for osteoporotic complications immediately after diagnosis). Future medical cost estimations derived from the PAID tool can be found in Appendix B4. For every cycle a patient aged *x* years is in life, the equivalent of 6 weeks future medical costs is charged based on annual costs of being alive aged *x* years. For all patients newly died, costs concerned to the final life year are charged for that year, and costs of being alive that were already charged in the previous 8 cycles (~ 1 year) were subtracted (otherwise patients would be charged costs of being alive and dying in the same year simultaneously). The number of newly died patients was calculated using the following equation:

$$Newly\ died\ patients = (1 - OS)_t - (1 - OS)_{t-1} \quad \text{(Equation 6)}$$

were *t* represents the current cycle, and *t*–1 the previous cycle.

Direct non-medical costs

Although literature on informal care demand in MM is scarce, the estimate of 10 hours per week fixed, used in the package advice daratumumab,[13] was considered inappropriate based on Ortega-Ortega *et al*.[60] A common preconceived view is that family life plays a more important role in southern European countries, and therefore it is often assumed that southern Europeans utilize more informal care, independent of actual need or demand for informal care. Such could, however, not be demonstrated in an analysis based on data from the Survey of Health, Ageing and Retirement in Europe, release 2.3.1. After correction for sociodemographic factors and patient characteristics such as ADL limitations and disease state (so presumably, all demand-determining factors were adjusted for), odds ratios (ORs) for transition to informal care in Spain and the Netherlands were 0.73 and 0.81, respectively (reference country: Belgium).[61] It is not possible to adjust hours of informal care utilization in the Netherlands with data from Geerts & Van den Bosch,[61] since ORs can inherently not inform on the magnitude of the effect. Hence, informal care utilization in this model could not be scaled with informal care use in Spain. Instead, it was assumed that all elderly MM patients in stable disease after first-line treatment demand an equivalent amount of informal care as Spanish MM patients in the second year after ASCT (weighted average 2.3 hours per day = 16 hours per week).[60] For patients progressed after first-line therapy, that is 5.3 hours per day (37 hours per week),[60] and finally for patients progressed after second-line therapy the demand is assumed to be the equivalent of patients pre-ASCT: 6.3 hours per day (44 hours per week).[60] Linear regression analysis in this study demonstrated that MM patients demand more informal care than

other blood cancer patients (lymphoma, acute leukemia, other disease). One hour of informal care was valued at €14.54 using the proxy good method recommended for Dutch analyses.[31]

Regarding transportation costs, it was assumed that most patients travel by car or public transport. According to the Dutch Cost Manual,[31] travelling by car and public transport should be valued with the same kilometer price (€0.20), and average parking costs are €3.12. Average distance to a general hospital in the Netherlands is 7 km.[31] Since travel distance for public transport in general is longer, and a base tariff is charged comparable to parking costs when travelling by car, total transportation costs per hospital visit were assumed to be €5.92 regardless of transportation mean. It was assumed that during a treatment scheme, diagnostics is performed simultaneously with the administration moments of drugs. The number of hospital is therefore based on the number of drug administration moments. If the option 'bortezomib administered at home' is selected, the average number of hospital visits saved (dependent on the percentage of bortezomib administrations that takes place at home) is subtracted from the total number of drug administrations, corrected for visits that remain necessary because of disease monitoring. During maintenance treatment or stable disease without anti-myeloma treatment, the number of hospital visits is based on the frequency of biochemistry assessment. In theory, blood tests can be performed more frequently than the outpatient hematologist follow-up consultations once per three months.

Indirect non-medical costs

It was assumed that productivity loss related costs do not apply to this disease population. The retirement age in the Netherlands is set to 65 years (and will be 67 in 2021). This implies that the lower bound of the disease population's age range at stake exceeds retirement age, also in the upcoming decade. Moreover, it was shown that almost all MM patients have sick leave immediately after diagnosis, and only 33% eventually return to work.[62] These data were collected in patients with maximum age of 55 years. Hence, it can be justified to assume that all patients have retired. In case patients were still working (which is a small percentage, of which a maximum of 33% returns to work), it is assumed that no differences between treatment arms with respect to return to work exist.

Total per-patient average costs were divided by total average health effects in QALYs accrued in all health states and presented as the incremental cost-effectiveness ratio (ICER). The ICER was compared to the societal willingness-to-pay (WTP) threshold. For MM, the estimated burden of disease is 0.71-0.79 (on a 0-1 scale), which classifies as the highest burden-of-disease class and therefore justifies a WTP threshold of €80,000 per QALY gained.[63]

Sensitivity analyses

Deterministic sensitivity analyses

To assess sensitivity of the model to individual parameter changes, one-way deterministic sensitivity analyses (DSAs) were performed. DSAs were carried out for variation in the parametric distributions for OS and PFS; input values for utilities for all health states; BSA and weight; parameters that have close relationship with the costs of daratumumab; vial sharing of daratumumab alone; vial sharing of daratumumab, bortezomib and carfilzomib; and home administration of bortezomib. The Excel model features the ability to vary the above parameters and run the model deterministically or probabilistically. Given the vast lack of literature on informal care use in MM, a DSA was also performed in which use of informal care was gradually increased in all three lines of treatment. Informal care time (in hours per week) was varied, while the valuation of one hour of informal care was kept constant.

Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed with the following parameters: biometrical patient characteristics; (dis)utilities; probabilities, duration and costs of adverse events; dosage and drug administration related expenses; healthcare resource use and costs, including costs related to third- and fourth-line treatment; and finally, transportation costs and informal care use and costs. Importantly, Dutch list prices of drugs were assumed to be fixed in the PSA. Gamma distributions were allocated to cost parameters, beta distributions to probabilities, and normal distributions to biometric patient characteristics, dose intensities and zoledronic acid dosage. If standard errors (SEs) were not provided in the original source, SE was estimated from the standard deviation (SD):

$$SE \approx \frac{SD}{\sqrt{n}}$$

If prices demanded inflation or conversion to another currency, the reported SE was converted to a percentage of the point estimate, and this percentage was also taken as SE for the inflated and converted price. When SD was not reported either, it was estimated with *range/6* if the range was provided.[64] Because of substantial discordance among reported utilities, SD of utilities was estimated with *range/4*,[64] where range was calculated as maximum utility minus minimum utility reported for a given line of treatment. If only an interquartile range (IQR) was reported, SD was estimated using:[65]

$$SD \approx \frac{q_3 - q_1}{1.35}$$

For probabilities of adverse events values for alpha and beta could be derived directly from ALCYONE and ASPIRE trial data, hence SEs were not needed. For remaining parameters for which no information

on variance around point estimates was reported, 20% of the mean for costs, and 10% of the mean for all other parameters were taken as SEs. By exception, 30% of the point-estimated utilization percentages of third- and fourth-line treatment regimens were taken for SEs, as these estimations were rather rough. Uncertainty around frequency of resource use during follow-up consultations was set to 5%, since monitoring frequency and use of diagnostics demonstrates a high grade of concordance among worldwide guidelines and protocols.[45,46,66] Values for SEs are reported in all tables as hard values or as a percentage (of the mean). Using alpha and beta values and allocated parameter distributions input values for all uncertain parameters were generated with Monte Carlo simulations. Random variables *Y* were generated for the shape and scale parameters of the parametric survival distribution, using the Cholesky decomposition of the covariance matrices of all parametric distribution, according to:

$$Y = \alpha \cdot C + p$$

Where α is the vector, randomly drawn between 0 and 1, C denotes the Cholesky decomposition matrix, and p is the baseline estimated value for the shape or scale parameter.

To explore the effect of random effects induced by using distinct distributions for OS in both arms on the CE-plane, the PSA was rerun using a joint modelling approach. In this alternative approach, the relative risk (RR) of death after median follow-up (16.5 months) was used as a proxy for the hazard ratio, because the latter was not reported. For each cycle, the proportion alive in the MPV arm was set to the proportion alive in the MPVD arm, multiplied with the RR. Although the proportional hazard assumption for OS was not met, this approach best allowed to assess the degree of uncertainty around effects that is induced methodically, but not in line with reality.

95% confidence intervals (CIs) corresponding to probabilistic ICERs were calculated using Fieller's theorem (Appendix A6).[67] If 95% CI bounds could not be calculated, uncertainty was expressed as the percentage of simulations below the WTP threshold of €80,000 per QALY gained.

Value-of-information analysis

To investigate the expected value of further clinical research to decrease decision uncertainty, a value-of-information (VOI) analysis was performed. The following explanation of VOI analysis and methods used is based on Appendix 3 in Hakkaart-van Roijen *et al*.[31]

Because of uncertainty around input parameters, and thus uncertainty surrounding the ICER, taking the wrong decision because of imperfect information comes with a loss of foregone benefits (the opportunity costs). Net monetary benefit (NMB) in the situation of perfect information, although hypothetical, can be compared to the NMB in the current situation of imperfect information. The difference is expressed

as the (per-patient) expected value of perfect information (EVPI) and indicates the value in monetary terms of reaching a state of perfect information. The EVPI can also be calculated for the entire disease population affected by the decision (PEVPI). The PEVPI effectively sets the upper bound to the value of further investigation to reduce uncertainty. To further guide future research, the contribution of individual parameters or groups of parameters to decision uncertainty can be assessed with the expected value of partial perfect information (EVPPI).

First, the EVPI was calculated using the results from the PSA analysis:

$$EVPI = mean(\max(NMB)) - \max\,(mean(NMB)) \qquad \text{(Equation 7)}$$

This EVPI was converted into a population EVPI as follows:

$$PEVPI = EVPI \cdot \sum_{k=i}^{T} \frac{N_i}{(1+\alpha)^{i-1}} \qquad \text{(Equation 8)}$$

where α represents the annual discount rate for costs (4.0%), N_i the number of patients affected by the decision in year i = 1, 2, … T. In this case, T was set to 5 years, since it is expected that within 5 years from now the pallet of treatment options has evolved to such extent that the decision at stake is not relevant any more. N_i was set to 176 based on estimations for the Dutch MM population over 70 year subjected to any first-line scheme in 2018,[13] and the assumption that 50% is treated initially with the MPV scheme.

EVPPIs were calculated for several parameters and groups of parameters (up to three parameters simultaneously), using the two-level Monte Carlo sampling algorithm featuring an inner and outer loop with j and k iterations, respectively. EVPPI calculations were performed with a self-made Excel macro (VBA script included in Appendix A7). Values for j and k were based on estimated computing time, and for the sake of time the number of PSA iterations was lowered to 500 for EVPPI calculations. Largest additional value of future research was *a priori* expected for costs of third- and fourth-line treatment, distribution of patients over advanced treatment schemes available, and informal care use.

Results

Variables

Patient characteristics

Biometrical patient characteristics that were taken into account are body weight and body surface area (BSA). Average patient weight was assumed to be 78 kg and average BSA 1.9 m^2.[68]

Utilities

An overview of utilities retrieved through the literature search is provided in Table 1. Most value was attached to utilities derived from European populations that preferably underwent the exact treatments of interest in this thesis. Therefore, the base case utility for stable disease during first-line treatment was set at 0.650. A systematic review by Golicki *et al*. demonstrated wide ranges of utility values for variation in severity of symptoms and phase of treatment,[42] which renders utilities for first- and second-line treatment being identical unlikely. For this reason, the utility for first-line treatment derived from the EMMOS registry was not taken into account. With respect to the utility for second-line treatment, there was only one article that provided a utility decrement for transition to second-line treatment. This resulted in an estimated utility of 0.592 for second-line treatment. Indeed, this is in line with the EMMOS registry findings, yet remarkably baseline utilities for US, Dutch and Belgian patients receiving second-line treatment are considerably higher. Besides, it is of note that the US data were based on the ASPIRE trial population receiving KRd, which corresponds to the second-line treatment in the present analysis. These deviations from 0.592 may be mainly explained by the fact that decrements for adverse events need to be subtracted from baseline utilities. Moreover, Dutch and Belgian data were sampled in patients that underwent ASCT, which indicates that, on average, this population was younger and fitter than the ASCT-ineligible population in this thesis. In sum, a second-line treatment utility of 0.592 was considered the estimate best reflecting the interpretation of the data in Table 1. Lastly, most articles reached a high grade of concordance regarding the decrement percentage for the transition to third-line treatment and beyond. A utility of 0.506 was estimated for the health state reflecting third-line treatment and beyond (fourth-line treatment, end-of-life/terminal care). Disutilities and durations for adverse events are in Appendix B1.

Table 1: Health state utilities

Reference	[33]	[33]	[24]	[69]	[27]	[28]	[25]	[70]
Population, questionnaire (Q), direct valuation method (DVM), if reported	ASPIRE trial population°, data on file from manufacturer: Q/DVM N/R	MM-002 trial population (pomalidomide alone or with dexa): EQ-5D, DVM N/R	Dutch, >66 yr, no distinction between treatment types	FIRST trial population (US, ASCT ineligible): QLQ-MY20 + QLQ-C30 + EQ-5D, DVM N/R	UK, median age 71, 4% <65 yr: EQ-5D, TTO	ASPIRE trial population°, direct EQ-5D + EORTC-QLQ-C30 (EQ-5D mapping US dataset	Dutch and Belgian patients, incl. ASCT, various ages: direct EQ-5D, DVM N/R	EMMOS registry: EQ-5D + EORTC-QLQ-C30 (EQ-5D mapping UK dataset), DVM N/R
First-line treatment								
Treatment	-	-		0.65	0.65*	-	-	0.59
Off treatment	-	-		-		-	-	-
Progression	-	-		-	0.59	-	-	-
Second-line treatment								
Treatment	0.82*	-		-	-	0.83*	0.81	0.59
Off treatment	0.84*	-	0.76	-	-	-	-	-
Progression	0.65*	-		-	-	0.66*	0.64	-
≥ Third-line treatment								
Progression (as proxy for utility of all advanced stages)	-	0.61		-	-	-	-	0.51
Adverse event decrement	-	0.08	-	-	-	Listed in article	Listed in article	-
Absolute progression decrement (reported)	-	-	-	-	-	0.17	-	-
Relative progression decrement (calculated)	21% (2>3)	N/A	N/A	N/A	9% (1>2)	20% (2>3)	21% (2>3)	14% (2>3)

*N/A denotes 'not applicable', N/R 'not reported' . Utilities marked with * were retrieved from patients treated with the exact same treatment schemes as applied in this analysis (MPV 1st line, Rd + carfilzomib 2nd line). °The ASPIRE trial population comprised patients from North-America, Europe and the Middle East; median age was 64, 46.7% was ≥65 yr.*

Estimated utilities for Dutch population (SE, distribution in PSA)	First-line treatment (stable disease)	**0.650**	**(0.0347, beta)**
	Second-line treatment (progression after first-line)	**0.592**	**(0.1250, beta)**
	Progression after second-line treatment	**0.506**	**(0.0709, beta)**

Costs

In Table 2, all cost categories and corresponding resources are displayed, along with the sources that were used to retrieve volumes and prices from. For readability, input values and detailed sources for medication-related costs are displayed all together in Appendix B2 (consecutively: CPIs and PPPs, treatment schemes, drug prices, drug administration costs). Costs related to management of adverse events and healthcare resource use costs are in Tables 3 and 4, respectively.

Table 2: Cost categories, resources and cost sources

Cost category	Resource item	Sources
Direct medical costs	Medication	
	Resources used	ALCYONE trial,[12] ASPIRE trial,[32] Dutch MM treatment guideline,[11] resource utilization evaluations,[10,48,54,58] package advice daratumumab.[13]
	Costs	www.medicijnkosten.nl[71]
	Administration of medication (day-care, out-/inpatient)	Delphi panel.[13,48]
	Adverse events and comorbidities	See references in Table 3; adverse event rates from ALCYONE[12] and ASPIRE[32] trials.
	Follow-up consultations	
	Resources used	NICE Guideline No. 35 – Myeloma: Diagnosis and Management (chapter 10: monitoring),[72] UMC Utrecht Myeloma guideline,[46] expert opinion.[45]
	Costs	See references in Table 4.
Indirect medical costs	Future medical costs	PAID tool (version 1.1, iMTA)[59]
Direct non-medical costs	Informal care	Ortega-Ortega *et al*. (2017),[60] Dutch Healthcare Cost Manual.[31]
	Transportation costs	Dutch Healthcare Cost Manual.[31]
Indirect non-medical costs	Productivity losses	N/A[62]

N/A denotes not applicable, AEs adverse events.

Resource use in advanced disease stages (third- and fourth-line treatment)

Latest data on resource use in the Netherlands in advanced myeloma were collected in 2011.[53] On average, monthly resource use costs excluding drug costs for third-line MM treatment amounted to €2,436 (inflated to 2018).[53] Another Dutch study found similar results, with average monthly resource use costs excluding drug costs of third and fourth-line treatment of €2,249 (inflated to 2018).[10]

Table 3: Adverse events rates and costs

Adverse event	Cost per event	SE	Distribution (PSA)	Price year (country)	Price inflated to 2018 (€)	MPV Rate	MPVD Rate	KRd Rate	Distribution (PSA)	Price source
Neutropenia	1,290.34	20%	Gamma	2015 (NL)	1,332.02	38.70%	39.90%	-	Beta	[13]
Anemia	1,808.39	20%	Gamma	2015 (NL)	1,866.80	19.80%	15.90%	-	Beta	[13]
Thrombocytopenia	3,400.38	20%	Gamma	2015 (NL)	3,510.21	37.60%	34.40%	-	Beta	[13]
Peripheral sensory neuropathy	769.22	20%	Gamma	2015 (NL)	794.07	4%	1.40%	-	Beta	[13]
Diarrhea	1,790.81	20%	Gamma	2015 (NL)	1,848.65	3.10%	2.60%	3.80%	Beta	[13]
Pyrexia*	US$ 1,455	US$ 207	Gamma	2005 (US)	1,562.78	0.60%	0.60%	1.80%	Beta	[73]
Nausea (Chemotherapy-induced nausea and vomiting)	US$ 778	20%	Gamma	2007 (US)	781.03	21.50%	20.80%	-	Beta	[74]
Pneumonia	3,952.34	20%	Gamma	2015 (NL)	4,080.00	4.80%	15.30%	-	Beta	[13]
Any infusion-related reaction	700.00	20%	Gamma	2018 (NL)	700.00	-	4.90%	-	Beta	[75]
Fatigue	711.16	20%	Gamma	2015 (NL)	734.13	-	-	7.70%	Beta	[13]
Hypokalemia	510.92	20%	Gamma	2015 (NL)	527.42	-	-	9.40%	Beta	[13]
Dyspnea	248.75	20%	Gamma	2015 (NL)	256.78	- -	-	2.80%	Beta	[13]
Hypertension	2,095.61	20%	Gamma	2015 (NL)	2,163.30	-	-	14.30%	Beta	[13]
Acute renal failure (+ dialysis)	US$ 11,016	US$ 280	Gamma	2012 (US)	9,605.03	-	-	8.40%	Beta	[76]
Cardiac failure**	CAN$ 16,899	20%	Gamma	2009 (CAN)	13,056.40	-	-	6.40%	Beta	[77]
Ischemic heart disease**	CAN$ 17,094	20%	Gamma	2009 (CAN)	13,206.82	-	-	5.90%	Beta	[77]

** Comprises diagnostic work-up for pyrexia with differential diagnosis, amongst others: febrile neutropenia, pneumonia, upper RTI, etc.; eventually resulting in diagnosis fever e.c.i. (e causa ignota).*
*** Costs are expressed per year. In the calculations, costs of these events are converted to costs per duration of the event (180 days for cardiac failure and ischemic heart disease)*

Table 4: Healthcare resource costs

Resource item	Frequency	Price (€)	Price year (country)	Price inflated to 2018 (€)	SE	Distribution in PSA	Source
Urinary light chain assessment	See Appendix C1	14.85	2015 (France)	15.35	20%	Gamma	[13]
IgA, IgG, IgM measurement (blood)	See Appendix C1	17.82	2015 (France)	18.42	20%	Gamma	[13]
Protein electrophoresis	See Appendix C1	14.31	2015 (France)	14.79	20%	Gamma	[13]
Biochemistry (CRAB)*	See Appendix C1	7.29	2015 (France)	7.53	20%	Gamma	[13]
Full blood count	See Appendix C1	30.83	2014 (NL)	32.02	20%	Gamma	[13]
Coombs test (only MPVD arm)	Prior to first daratumumab gift	3.62	2017 (NL)	3.67	20%	Gamma	[78]
Bone marrow aspiration and assessment	See Appendix C1	325.66	2018 (NL)	325.66	20%	Gamma	[79]
Hematologist visit	See Appendix C1	132	2014 (NL)	137.08	20%	Gamma	[13]
Whole body PET-CT	See Appendix C1	1,148.64	2014 (NL)	1,192.86	20%	Gamma	[80]
General practitioner (blood pressure monitoring)	Once per two weeks during KRd	33	2014 (NL)	34.27	20%	Gamma	[31]
* *CRAB = Calcium, Creatinine [Renal], Hb [Anemia], and Bone lesions [via imaging])*							

More recent, French data from 2015 show that third to fifth-line therapy monthly costs amounted to €886 on average (drug costs excluded and corrected for purchasing power).[54] Despite French data being more up-to-date, more value is attributed to the Dutch findings with respect to healthcare utilization in advanced myeloma in this analysis. It is assumed that healthcare utilization in third and fourth line remains €2,436 per month excluding drug costs.[53] Since drug costs were expressed as the contribution to mean monthly costs in Gaultney *et al*., it is impossible to derive monthly drug costs per treatment regimen from this study.[10] Drug costs were estimated as follows.

The guideline recommendation to add alkylating agents (e.g., REP) immediately after patients are deemed ineligible for participation in any advanced myeloma clinical trial,[11] is not appropriately reflected in the estimations made by the hematologist panel. Guideline recommendations and expert opinion were therefore combined to make predictions on the average distribution of patients over various options for third- and fourth-line therapy until death (Table 5). Drug-related costs of advanced lines of treatment collected in France were inflated to the current Dutch price level. These costs were compared to costs calculated for the Netherlands, and since costs were concordant, Dutch costs were taken as input values (Appendix B2, 'Other resources used'). Costs of daratumumab monotherapy were firstly calculated with the following assumptions: daratumumab is dosed at 16 mg/kg once per week for 8 weeks, followed by once per two weeks for 16 weeks, and finally once per four weeks until progression.[11] A recent trial demonstrated that median OS under daratumumab monotherapy is 20.1 months.[81] So, it is assumed that the average monthly dosing frequency is 1.5 (the weighted average over 20 months). Costs of daratumumab monotherapy were then compared to the calculations in the MSc thesis of M. de Weerd. Both calculation demonstrated a fair degree of concordance, but since it should be able to take the setting 'vial sharing for daratumumab?' into account, the input value that followed from the calculation in this thesis was used. Other healthcare resource use under daratumumab monotherapy was assumed to equal that of the other three treatment regimens. Patients receiving best supportive care without actual anti-myeloma drugs were charged the same amount for other healthcare resource use, but no additional drug costs.

Table 5: Third- and fourth-line treatment regimens

Treatment regimen	**Initially MPVD**	**Initially MPV**
Daratumumab monotherapy	-	28%
POM-DEX	49.6%	32%
BOR-DEX	24%	16%
Rd/REP	6.4%	4%
Not receiving anti-myeloma treatment (best supportive care)	20%	20%

POM denotes pomalidomide, DEX dexamethasone, BOR bortezomib, Rd lenalidomide + dexamethasone, REP lenalidomide + cyclophosphamide + prednisone. Best supportive care also comprises end-stage MM patients receiving terminal care.

Cost-effectiveness

Median estimated OS in the model was 12.7 (inter quartile range [IQR] 3.8–18.2) and 9.6 (IQR 3.7–18.3) years in the MPVD and MPV arm, respectively. Median OS was not reached in the ALCYONE trial. Median PFS in the model was 2.8 (IQR 1.3–5.2) and 2.3 (IQR 0.7–2.7) years, respectively. In the ALCYONE trial, median PFS in the MPVD arm could not be reached (but at least exceeded 2.3 years), and median PFS in the MPV arm was 1.5 years. Notably, estimated median PFS in the model is 53% larger than empirically established. Hence, incremental effects are probably underestimated in the model. Table 6 summarizes the main outcome measures regarding effects, including mean OS (expressed as average life years gained).

Table 6: Main average per-patient effects

Arm	Life years gained	(Net) QALYs gained	QALYs lost due to AEs in first-line treatment
MPVD	10.15	5.75	0.037
MPV	9.42	5.16	0.047
Increments	**0.73**	**0.59**	**– 0.010**
QALYs denotes quality-adjusted life years, AEs adverse events. Only effects of adverse events in the MPV(D) scheme are displayed in this table.			

Total average per-patient costs by cost category are displayed in Table 7. All costs displayed in this table underwent discounting. In the actual model cost strata were not subjected to distinct discounting; only total costs per cycle were discounted. Apart from positive incremental costs related to drugs, MPVD logically comes with increased future medical costs, since OS in the MPVD arm exceeds OS in the MPV arm. On the contrary, modest savings were achieved with respect to healthcare resource use and costs of informal care.

Table 7: Average per-patient costs by category

Arm	Drug-related costs (only MPV[D] and KRd)	(Other) healthcare resource use and management of adverse events	Future medical costs	Informal care and transportation costs	Total costs
MPVD	€688,454	€458,646	€122,470	€207,823	**€1,477,394**
MPV	€366,357	€540,712	€115,840	€218,569	**€1,241,478**
Increments MPVD vs MPV	**€322,097**	**– €82,066**	**€6,630**	**– €10,746**	**€235,916**

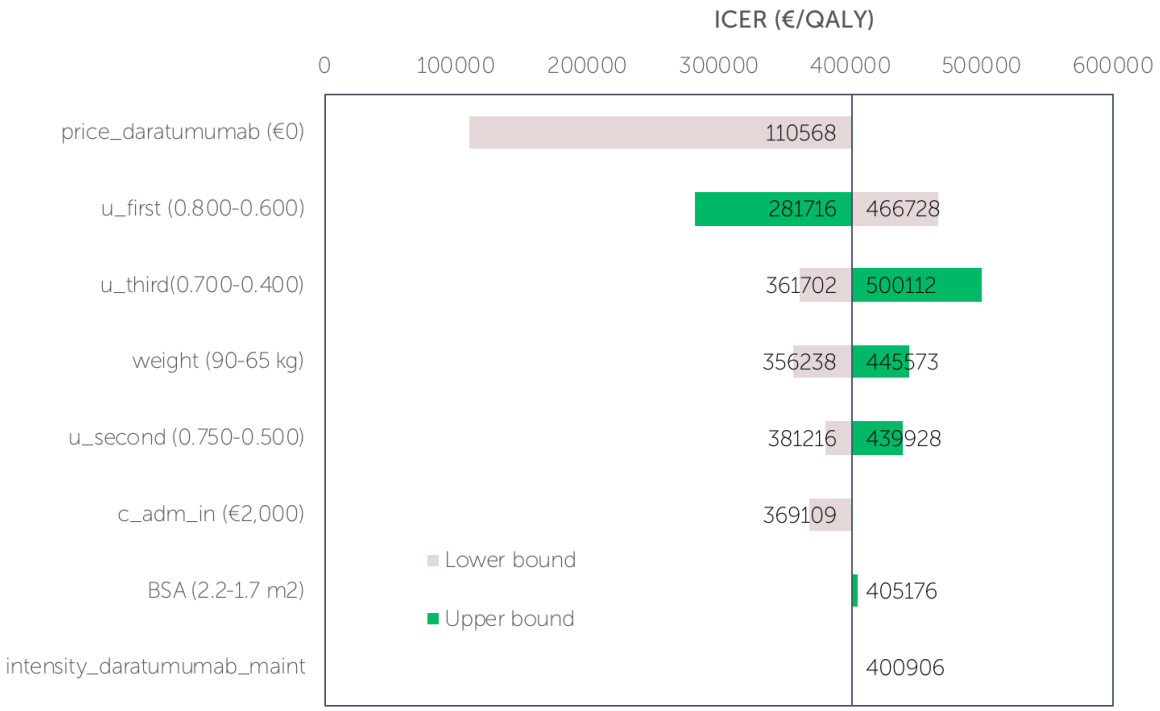
In the deterministic analysis, the ICER is €400,906 per QALY gained. The ICER is almost exclusively driven by drug-related costs, far and foremost through drug costs of daratumumab, and to a much smaller extent through higher drug administration costs because the MPVD is more intensive in terms of drug administration moments.

Sensitivity analyses

Deterministic sensitivity analyses

The results of most DSAs are shown in Fig. 4. Compared to other parameters, utilities have a strong influence on the ICER. Although most dosages (bortezomib, melphalan, corticosteroids) are based on BSA, this parameter has a negligible effect on the ICER. Variation in body weight, in contrast, has a significant effect, since daratumumab is dosed per kg of body weight. Relative dose intensity (the

Fig. 4: Tornado diagram illustrating effects of variation in various parameters



Legend:

price_daratumumab	Price of 1 vial (5 ml = 100 mg) daratumumab
u_first	Utility of health state reflecting first-line therapy
u_second	Utility of health state reflecting second-line therapy
u_third	Utility of health state reflecting progression after second-line therapy
weight	Average body weight
c_adm_in	In-hospital administration costs of (intravenous) anti-myeloma drugs
BSA	Average body surface area
intensity_daratumumab_maint	Relative dose intensity of daratumumab during maintenance therapy

fraction of the initially intended dose that was actually administered) during maintenance therapy had no effect on the ICER, and neither does relative dose intensity in the first to ninth treatment cycle (data not shown). It is of note that even at a price of €0 per vial for daratumumab, the ICER is still above

Fig. 5: Scenario analyses

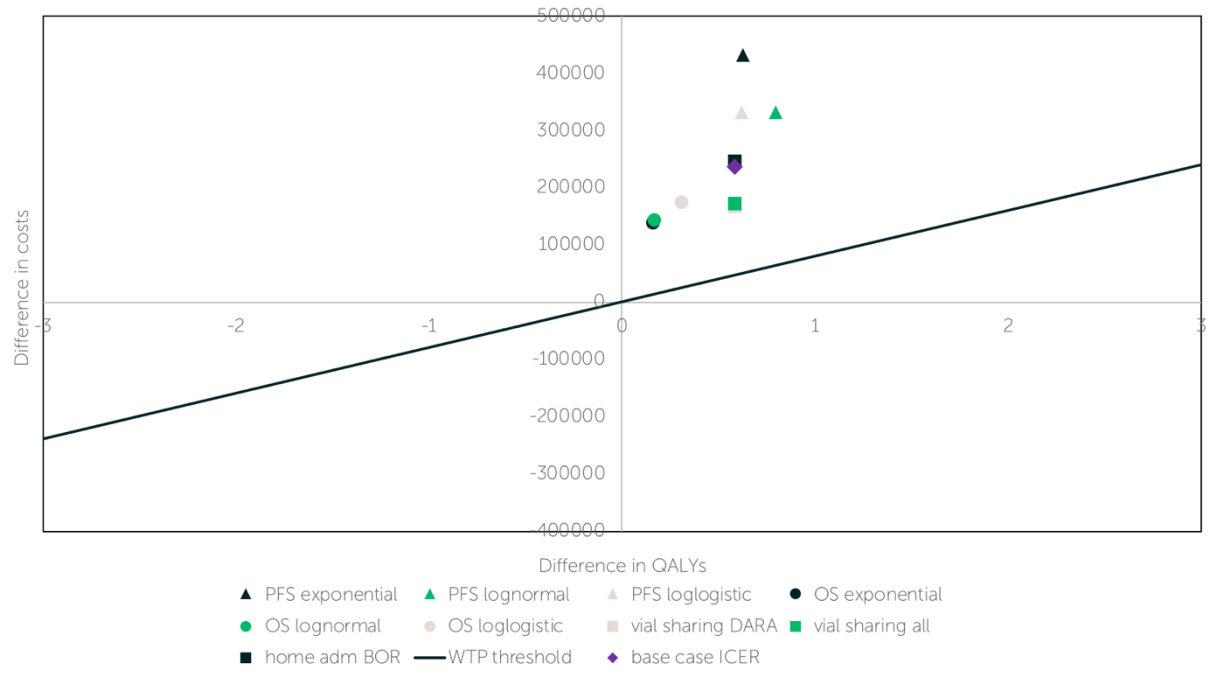
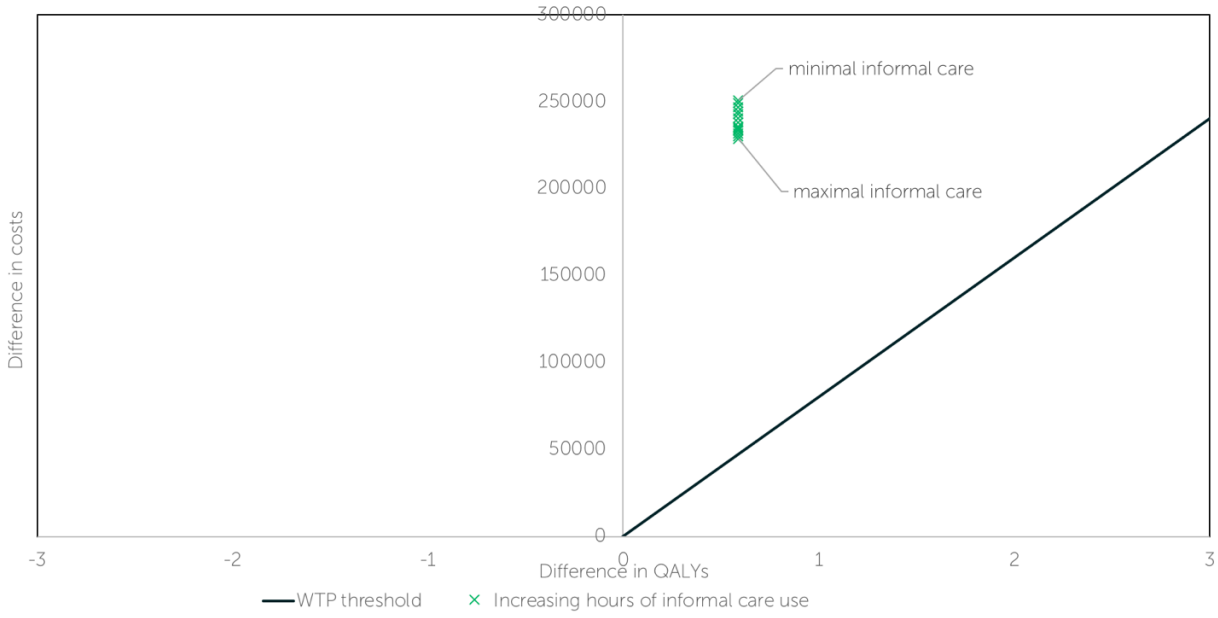


Fig. 6: Variation in informal care use



€100,000 per QALY gained, because the MPVD is more intensive in terms of hospital visits and drug administration moments. Even a decrease by approximately 50% of the in-hospital administration costs has no relevant effect on the ICER. Fig. 5 demonstrates the effect of variation in parametric distributions for OS and PFS, as well as the effect of vial sharing of daratumumab alone ('DARA'), or daratumumab, bortezomib and carfilzomib together ('all'). Finally, the effect on the ICER in case bortezomib is administered at home (under the assumption that 60% of total bortezomib administrations takes place at home) is predicted. Although home administration of bortezomib can theoretically decrease hospital resource use drastically, this alternative scenario hardly affects the ICER. In dark green is the societal WTP threshold (€80,000 per QALY gained). None of the isolated scenarios renders an ICER below the WTP threshold, neither does any combination of different scenarios (e.g., vial sharing of all agents in combination with another distribution for OS; data of combined scenarios not shown for readability). Fig. 6 shows the results of the DSA in which the amount of informal care use has been gradually increased, starting at 10 hours weekly for all stages, up to the base-case input values (16, 37, and 44 hours a week for first-, second- and third/fourth-line, respectively). Table 8 reports the RR for death after median follow-up that was calculated to facilitate a joint modelling approach for OS. This alternative approach yielded a deterministic ICER of €449,473 per QALY gained.

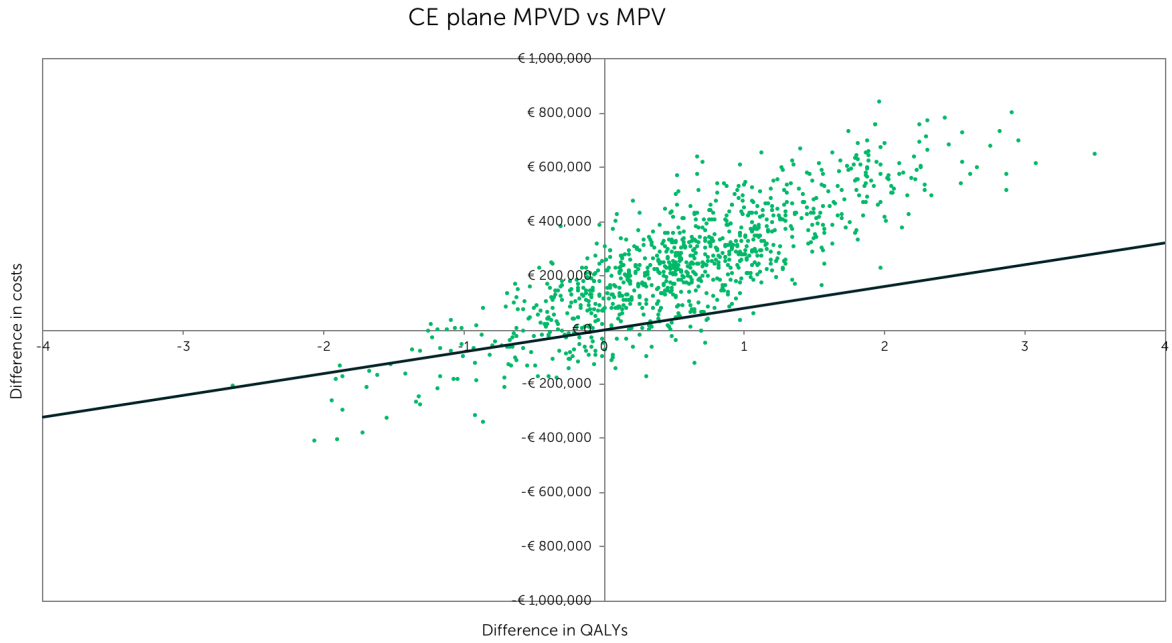
Table 8: Deaths and RR for death in MPV as compared to MPVD

Arm	**N (Intention-to-treat)**	**Deaths**	**$RR_{MPV\ vs\ MPVD}$**
MPVD	350	45	1.0487
MPV	356	48	

Probabilistic sensitivity analyses

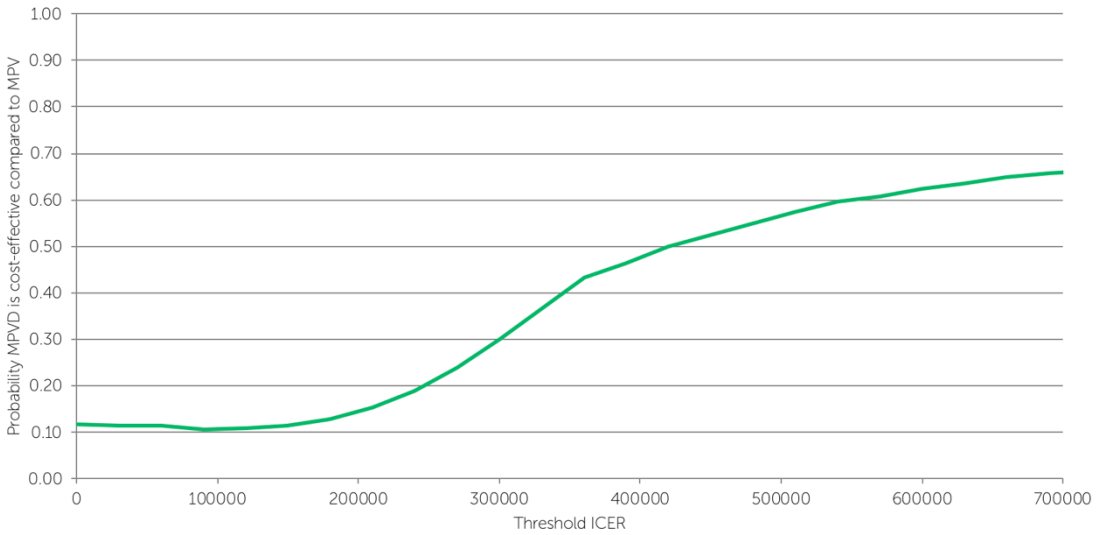
The PSA yielded a probabilistic ICER of €418,928 per QALY gained. The incremental cost-effectiveness plane (CE plane) that resulted from the PSA is displayed in Fig. 7. 75.4% of the PSA simulations is in the right-upper quadrant, indicating that MPVD comes with improved health effects, but also with higher costs. When the usual WTP threshold is respected, there is a 11% chance that MPVD is cost-effective compared to MPV (Fig. 8). However, only 3.5% of all PSA simulations yielded an ICER below the WTP threshold *while* incremental health effects were positive. The maximum chance of MPVD being cost-effective over MPV is 70% (when the WTP threshold approaches infinity). The interpretation of these percentages will be discussed into further detail in the discussion section. In the alternative approach (joint modelling for OS), the probabilistic ICER was €488,390 (95% CI: –15,445 – 1,701,181) per QALY gained (MPV is dominated by MPVD at the lower limit of the CI). The corresponding CE-plane and CEAC are displayed in Appendix B4.

Fig. 7: CE plane for MPVD vs MPV



The line in dark green reflects the societal willingness-to-pay threshold (€80,000 per QALY gained).

Fig. 8: Cost-effectiveness acceptability curve



The cost-effectiveness acceptability curve informs on the chance that adopting the new MPVD scheme is cost-effective given a certain willingness-to-pay threshold.

Value-of-information analysis

At the usual WTP threshold, the per-patient expected value of perfect information is €8,143 (Fig. 9), which translates to a population-based EVPI of €6,635,543 for an effective decision life time of 5 years. Although additional information gathered through more research would be of considerable value given the high PEVPI, guidance for future research cannot be provided despite multiple EVPPI analyses (Table 9).

Fig. 9: Per-patient EVPI against WTP threshold

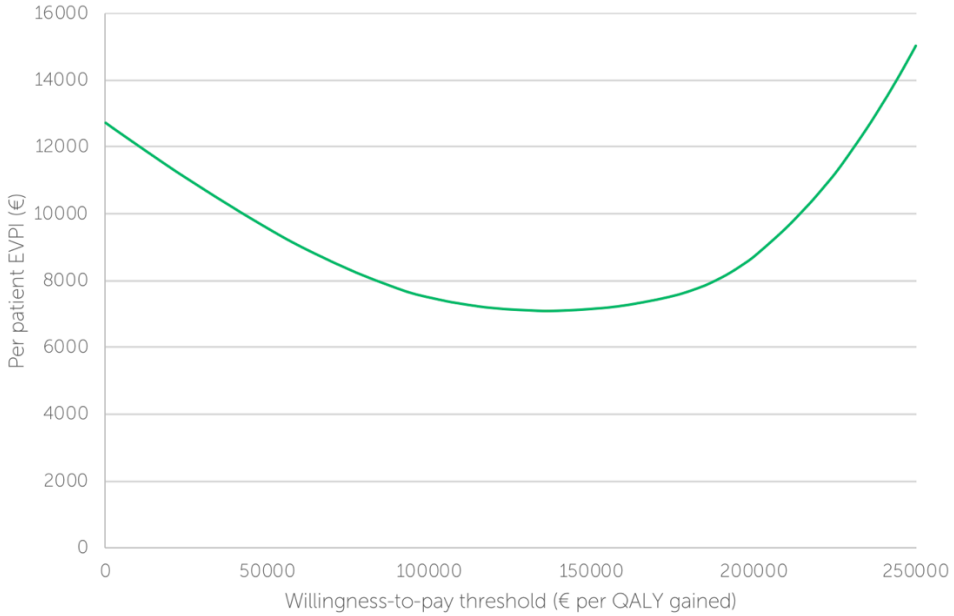


Table 9: EVPPI analyses

Parameter(s) fixed	**Inner loop iterations (*j*)**	**Outer loop iterations (*k*)**	**PSA simulations**	**EVPPI**
inf_care3	20	20	500	€0.00
inf_care1, inf_care2, inf_care3	20	20	500	€0.00
f_pomdex_dara, f_bordex_dara, f_rep_dara	20	20	500	€0.00
c_pomdex, c_bordex, c_rep	20	20	500	€0.00
u_first, u_second, u_third	20	20	500	€0.00
c_adm_in, f_adm_in	20	20	500	€0.00

Legend:

inf_care1	Hours of informal care used per week during/after first-line treatment
inf_care2	Hours of informal care used per week during/after second-line treatment
inf_care3	Hours of informal care used per week after progression on second-line treatment
f_pomdex_dara	Fraction of patient receiving a POM-DEX regimen in third/fourth-line treatment
f_bordex_dara	Fraction of patient receiving a BOR-DEX regimen in third/fourth-line treatment
f_rep_dara	Fraction of patient receiving a Rd/REP regimen in third/fourth-line treatment
u_first	Utility of health state reflecting first-line therapy
u_second	Utility of health state reflecting second-line therapy
u_third	Utility of health state reflecting progression after second-line therapy
c_adm_in	Drug administration costs of in-hospital administration
f_adm_in	Fraction of patients receiving their (intravenous) anti-myeloma drugs during clinical admission.

Discussion

Key findings

This cost-effectiveness analysis demonstrates that addition of daratumumab to the MPV induction scheme for MM is, considering a WTP threshold of €80,000 per QALY gained, with 89% certainty not cost-effective at a deterministic ICER of €400,906 per QALY gained. Major cost drivers are drug price of daratumumab, and wastage of drug leftovers, especially of daratumumab. Alternative parametric distributions for survival extrapolation without exception lead to an increased ICER. Even at a per-vial price of €0 for daratumumab, addition of daratumumab from a societal perspective is not cost-effective, due to higher future medical costs and more frequent healthcare resource use in the MPVD scheme. To reduce the chance of taking the wrong decision to not reimburse daratumumab for first-line treatment, a maximum amount of €6,635,543 should be invested in further research. This analysis failed at guiding research topics that are expected to be most contributive in decreasing uncertainty.

Economic evaluations focused on daratumumab are utterly scarce. The current analysis is the first to assess the cost-effectiveness of first-line application of daratumumab. Previous cost-effectiveness analyses from a Dutch societal perspective for application of daratumumab after at least one prior line of treatment demonstrated considerably lower ICERs: €56,830 to €109,742 per QALY gained for VdD and €129,721 to €338,087 per QALY gained for RdD.[13] Although the ICERs of these analyses suggest that the ICER of first-line daratumumab is realistic, direct comparison of ICERs would not be methodologically sound. Effective lifetime in the population undergoing first-line treatment is for instance longer than in patients suffering from relapsed or refractory MM. This affects cumulative treatment costs of daratumumab-containing regimens, since daratumumab is continuously administered during maintenance therapy. Uncertainty in the present study was expressed based on probabilistically calculated ICERs. Dutch studies on RdD and VdD, on the contrary, took upper and lower bounds of deterministic ICERs to express uncertainty. These ranges cannot be compared to each other, yet visual inspection of the CE planes reveals that in general results of the VdD and RdD studies are less uncertain than results of the current study, mainly regarding costs. Another, 2018 cost-effectiveness analysis from a U.S. health sector perspective studying second-line application of daratumumab calculated an ICER of $101,108 per QALY gained for VdD compared to Vd, and $187,905 per QALY gained for RdD compared to Rd.[33] At the maximum WTP threshold of $150,000 per QALY gained, the VdD scheme was cost-effective with 87% certainty; the RdD scheme was dominated for any WTP threshold.[33] These results are concordant with Dutch findings in second-line treatment, but again do not permit any inferences to be made with respect to first-line treatment. Finally, another American study concluded that in heavily pre-treated MM (median five prior lines of treatment), carfilzomib and pomalidomide-containing regimens entirely dominate daratumumab monotherapy across all WTP thresholds.[82]

NICE has recommended daratumumab monotherapy within the Cancer Drugs Fund since last January. In Germany, daratumumab has also been included in Appendix XII of the *Arzneimittel-Richtlinie.* Within early lines of MM treatment, medical practices of European hematologists are concordant across Europe.[83] It is expected, therefore, that in near future other European countries will be faced with daratumumab moving from refractory myeloma to earlier lines of therapy. Based on the decision chart for transferability constructed by Welte *et al*.,[84] the current analysis passes all initial knock-out criteria (technology comparability, relevance of the comparator, quality of the analysis). Although other countries may set different requirements to, for instance, the perspective of the analysis, results from this analysis can be informative: incremental costs are mainly made directly within the healthcare sector. Hence, irrespective of the perspective, this thesis provides a sense of the cost-effectiveness of daratumumab introduced in the first-line MPV induction scheme.

Dutch policy implications

Recommendations for clinical practice

Extrapolated health effects in this analysis are rather modest compared to the empirically established hazard ratio for disease progression or death in the ALCYONE trial (HR = 0.50 [95% CI: 0.38–0.65] versus 5.75 QALYs, of which 0.59 incremental, gained over a median lifetime of 12 years in the MPVD arm). All distributions fitted to survival data proved relatively incompatible with empirical data, which may explain the large difference between hazard ratio and incremental health effects. Extrapolation of survival curves will be discussed into further detail below. It was beyond scope to investigate possible prognostic effects of prolonged PFS, apart from immediate health effects for the patients. In the short run, addition of daratumumab to the MPV induction scheme in ASCT-ineligible MM patients proved beneficial to extending PFS. However, given high costs concerned with addition of daratumumab, it is recommended not to use the MPVD scheme until daratumumab is reimbursed for combinations schemes. This is in line with latest HOVON recommendations to save daratumumab-containing combination schemes in second line (VdD and RdD) until daratumumab is removed from the 'drug lock'.[85] Apart from the reimbursement argument, MPVD – in contrast to RdD and VdD – has not yet been assigned an official indication in the latest update of the Dutch treatment guideline,[85] nor in the Dutch pharmacotherapeutic database (*Farmacotherapeutisch Kompas)*.[86]

Reimbursement recommendations

The addition of daratumumab to the MPV induction scheme for ASCT-ineligible MM patients is not cost-effective. Moreover, price negotiations apparently cannot immediately influence the reimbursement decision, since even at €0 per vial of daratumumab, MPV remains cost-effective. Therefore, it is not recommended to include daratumumab as a first-line agent in the basic benefit

package. Nevertheless, in the near future it may be worthwhile to revisit the cost-effectiveness analysis of first-line daratumumab if shifts in second-line treatment practices have acted out, especially if ALCYONE follow-up data allow head-to-head comparison of second-line RdD after MPV to KRd after MPVD. A budget impact analysis is lacking in this thesis, but when multiplying incremental costs (€235,916) with the upper limit of the estimated number of annual MM patient eligible for MPVD (176), total budget impact would amount to €41 million, or approximately 0.04% of Dutch healthcare expenditures. This share to total healthcare expenditures equals to 1% of total GP or total dental care expenditures, by example.[87] Beyond any reasonable doubt this would pose a threat to public health, as it could crowd-out health demands at a population level.

Strengths and limitations

A number of strengths can be identified in this study. The greatest advantage is that the model features distinct health states for first-, second- and third/fourth-line treatment. Achievements regarding OS have been very good since the introduction of bortezomib and lenalidomide as first-line agents,[88] and therefore it has become more difficult to statistically significantly demonstrate differences in OS nowadays.[89] Clinically relevant improvements are currently being achieved mainly through extended PFS and shorter time to response. To adequately quantify health effects after progression under first-line therapy, it is essential to model consequent treatment lines, especially if outcomes of consequent treatment are depended on what first-line treatment scheme was administered. This study anticipates the long-term follow-up results of the ALCYONE trial. With few adjustments to the model, it is possible to run the model with detailed information on second-line treatment outcomes after induction with MPVD or MPV. In this way, inter-arm differences in HR-QoL and time-to-consequent-treatment can be maximally respected. For future research, it is recommendable to model lines of treatment to the best attainable detail.

The field of MM (and hematology in general), is rapidly changing. Innovations such as home administration of bortezomib can have a serious influence on costs of bortezomib-containing regimens, and through second order effects also on related treatment schemes. It has recently been shown that often hematologists adopt new treatment strategies in daily practice immediately after publication of primary literature and drug approval.[90] Therefore, another strength is that this model can provide fit-for-future predictions, since options for several scenario analyses are facilitated in a user-friendly way. In this way, effective lifetime of decisions made with the model is maximized.

Lastly, basic cost-effectiveness analyses have been extended with value-of-information analyses. These analyses failed to guide future research, since all EVPPIs were €0.00. EVPPI calculations could be improved in two ways. One option is to increase the number of inner and outer iterations (j and k), which raises a trade-off against computing time. To maximize efficiency, ideal values for j and k can be

determined by estimating bias and 95% CIs in a small sample of the parameter(s) of interest prior to actual EVPPI calculations.[91] Another option is to apply the regression-based EVPPI calculation method with results from the PSA described by Strong and colleagues.[92] Unfortunately, this web application demands PSA results to be delivered in a specific way, which was unattainable before the thesis deadline. Importantly, the population-based EVPI was based on the Dutch population. In reality, research is often performed in international collaborations and clinical practice is rather similar in Western Europe and the United States, so the actual PEVPI is even higher. What PEVPI and EVPPIs do inform on, is that uncertainty surrounding the base case ICER is large, but uncertainty is not specifically driven by a single subset of parameters. It is possible that part of the uncertainty is due to population heterogeneity.[93] Patient heterogeneity and parameter uncertainty should be distinguished with stratified analyses,[93] but it was beyond the scope of this study to identify predictors of, for instance, informal care use, that can define distinct strata. Besides, it is probably impossible to predict prospectively what third- or fourth-line scheme a patient will be treated with, so for a number of uncertain parameters stratified analyses are impossible and not practically informative by definition. Future research should focus on resource use in advanced myeloma (particularly inter-arm differences between MPVD and MPV and application of daratumumab monotherapy), as well as HR-QoL under MPV compared to MPVD, and acquiring more mature survival data.

The design of the present study also comes with some limitations. Firstly, utilities had to be estimated based on a variety of sources. The utility for second-line treatment used in this study is 25% lower than the utility for the same disease state used in the CEAs included in the 'package advice'.[13] A sceptic explanation for this discordance is that it is advantageous to Janssen-Cilag if the utility for PFS under second-line treatment is overestimated. The company was, however, transparent on its methods for data collection: it based its utility estimations on QoL data from the CASTOR trial, in part also for the cost-effectiveness analysis belonging to the POLLUX trial. Therefore, deviations can also be explained in a way that utilities in this study have been underestimated; high utilities reported for second-line treatment at least suggest such.[25,28,33] Another limitation is that utility decrements for adverse events had to be retrieved from literature on entirely different diseases than MM. The same adverse event may have a different impact on HR-QoL, depending on underlying disease. Besides, from a clinical point of view, duration as reported in literature of some adverse events is debatable. Sensory peripheral neuropathy, for instance, is irreversible, so a duration of 180 days (even if the authors consider 180 days the mean duration) is not realistic. An alternative method is to perform OLS regression with HR-QoL data and calculate utilities with the regression coefficients, e.g., for adverse events, progression and hospitalization.[94] Until additional data on the ALCYONE population is available, this method cannot be applied. Apart from single events (progression, adverse events), even in stable disease, HR-QoL may diminish with time due to cumulative symptom burden.[95] In this respect, it is of note that the typical remission-relapse pattern of MM (Fig. 10) and time-to-response have been neglected in the present

study. In contrast to applying just one utility for each health state, real life could have been approached closer if time-dependent utilities based on the typical disease pattern had been used.

Fig. 10: Characteristic remission-relapse pattern of MM

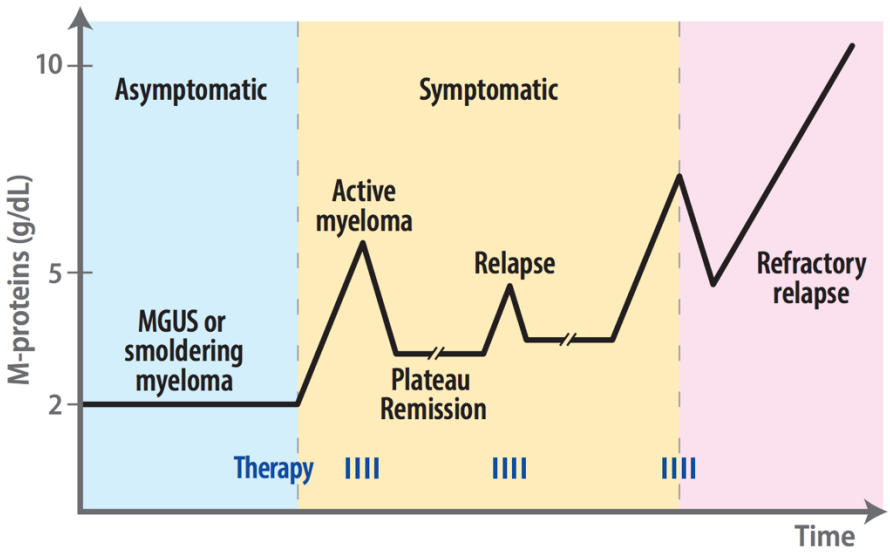


Figure reused from Durie.[96]

Secondly, direct Kaplan Meier curve digitization from a raster image may have diminished quality of survival data used in the analysis. Although the resolution of the reader was matched to the thickness of the survival curves to prevent confusion with patient censor marks, individual patient-level data could only be estimated using interval numbers at risk. Because of the high degree of censoring, clinical validity of the distributions used for extrapolation demands emphasis over statistical fit.[97] At the same time, prediction of long-time (progression-free) survival in MM is a difficult undertaking, even for medical specialists.[13] Furthermore, extrapolation was carried out with only a limited number of parametric distributions. For time constraints, only the R package *survival* was used, but other R packages such as *flexsurv* also include a Gompertz distribution, and the more sophisticated Royston-Parmar spline model.[98] The Kaplan Meier curves for PFS in both arms demonstrate an increasing descending course, which proved imperfectly compatible with either of four distributions used in this study. A piecewise model, like the spline model, could possibly appreciate real-life PFS to a better level in a parametric extrapolation. Moreover, extrapolated OS and PFS are associated with uncertainty; even with fixed utility values, incremental QALYs ranged from –1 to +1.5. It was demonstrated that as a rule-of-thumb uncertainty around mean survival gets close to zero when follow-up time is sufficient to establish median survival.[99] It follows from Appendix B4 that a joint modelling approach targeting methodologically induced uncertainty can drastically reduce the size of the CE-plane. Future analyses should examine which of both approaches is best compatible with extended ALCYONE survival data.

As discussed above, realistically, there is little time to wait for more mature survival data, since the decision will rapidly become less relevant (or even irrelevant) with time. Indirect comparisons via network meta-analyses could be a solution,[100] but for the case of daratumumab applied in first-line therapy, no other similar comparators are at hand. A Bayesian approach could partly solve for the lack of more mature data. Based on prior daratumumab trials, it is very unlikely that addition of daratumumab leads to negative incremental health effects. If simulations with negative health effects are excluded from the analysis, MPVD has a 5% chance of being cost-effective at a WTP threshold of €80,000 per QALY gained (data not shown in DSA figures). Apart from general uncertainty due to limited follow-up time, the number of patients progressing towards second-line treatment is overestimated, since in- and outflow of patients in second-line treatment could not be distinguished. As a result, the number of patients in third- and fourth-line treatment is overestimated, which probably caused the ICER to decrease. Furthermore, latest data on survival of the general population available to this study dated from 2015. Maximum survival of MM patients could be slightly underestimated, if the absolute life expectancy cap indeed was too strict.

A third limitation is that within second-line treatment only one regimen (KRd) was assumed. This assumption was based on the recommendation that a three-drug regimen prevails, especially in patients with clinically important symptom burden. However, in patients that prefer a scheme with oral administration only, Rd + ixazomib is the scheme of choice. Moreover, given serious risks of cardiovascular adverse events under carfilzomib, individual patient characteristic regarding medical history are essential in making a choice for second-line therapy. For these patients – and perhaps for all patients in future – daratumumab instead of carfilzomib is suggested, albeit only if daratumumab is reimbursed for that indication.[11] It would be informative to model stratified data (only patients previously treated with MPV) from the POLLUX trial (Rd + daratumumab after at least one prior line of therapy) and make a distinction between the MPV and MPVD arm in second-line treatment schemes. However, for a lack of head-to-head comparisons between Rd + daratumumab (RdD), Rd + ixazomib and Rd + carfilzomib (KRd), it would be challenging to establish incremental survival effects with sufficient certainty. Indirect comparisons demonstrated that PFS was approximately doubled with daratumumab (hazard ratios for PFS as compared to Rd were 0.37, 0.74 and 0.69, respectively).[11]

Fourthly, ranges of uncertainty that were used in the PSA could be criticized. Future medical costs were assumed not to be uncertain, as follows from the results returned by the PAID tool. When using the PAID tool, however, volumes rather than prices of future medical costs should be considered uncertain.[(1)] Uncertainty regarding 'volume' *de facto* is reflected in the uncertainty surrounding extrapolated survival effects. Another point of discussion is the ranges of uncertainty that were applied

[1] I discussed this with Dr Pieter van Baal.

in general. It is generally accepted to apply ranges of 10% or 20% to parameters for which SDs are unknown. This study tried to apply uncertainty ranges that were based on available data as much as possible. For instance, SDs were not present for all utilities, but realistic ranges of uncertainty were estimated using the full range of reported values. On the contrary, for some parameters SDs were actually reported, but point estimates for these values were sampled in a setting totally different from Dutch 2018 healthcare. For example, costs of acute renal failure were retrieved from a 2012 U.S. source. Because of the large study size (n = 29,763,649), SE was a 10-fold smaller than the 20%-of-the-mean estimation for SEs. Yet, if the SE from another source (especially sources from abroad) is used in the PSA, it is implicitly suggested that costs are perfectly comparable. Medical practice is, however, strongly influenced by country-specific preferences, of which the existence of national guidelines is the testimony. Conceivably, uncertainty is underestimated if SEs are just taken from an international source and applied to a different national context.

Fifthly, a very recent micro-costing study on differences between intravenous (IV) and subcutaneous (SC) administrations costs of oncology drugs gives rise to revising drug administration costs.[101] This study demonstrated differences between costs of IV and SC administration mode (€90 and €180 depending on the drug),[101] which has not been taken into account in this study. In absolute terms, administration costs were also lower than estimated in this study (€117 and €207 depending on the drug, as opposed to €357 in this study). Just prior to submission of the thesis, a supplementary DSA was performed with outpatient (day-care) drug administration costs set to €117 and frequency of inpatient administration set to 5%. This scenario resulted in a decrease of the deterministic ICER to €349,004 per QALY gained.

Final thoughts on the interpretation of results

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HOVON guideline recommendations are updated on a regular basis, based on latest scientific insights.[85] This also has implications for consultation of the results of this cost-effectiveness analysis. Although it was attempted to devise a model in which expected changes in the field can be easily implemented, not all potential future game changers could be reckoned with. Some examples are – although vastly under-researched – the role of magnetic resonance imaging (MRI) as a complementary imaging mode, or even a successor of positron emission tomography/computed tomography (PET/CT),[102] osteoporosis prophylaxis with six-monthly denosumab instead of four-weekly zoledronic acid,[103] and minimal invasive cytology via serum sampling of tumor DNA to monitor disease course.[104] "Whole-body" MRI, subcutaneous denosumab and serum DNA sampling are each by each less labor-intensive and less expensive than their corresponding complements that are currently used in daily practice, and could therefore affect the ICER, and budget impact of MM treatment in general. It is advisable to review latest

literature when this thesis is consulted, to assure the therapeutic landscape as outlined in this thesis is up-to-date.

Willingness-to-pay vs willingness-to-accept threshold

It follows from the PSA analysis that 11% of simulations were below the societal WTP threshold, yet only 3.5% of simulations resulted in positive incremental effects while simultaneously being below the threshold. It is essential to understand that the 11% calculation assumes society is willing to accept a loss in clinical effectiveness – as long as it also comes with a decrease in costs of at least €80,000 per QALY lost. A substantial degree of disparity is present between WTP (for increased health effects) and WTA (for foregone health effects), however (Fig. 11). A meta-analysis found a WTA/WTP ratio for health and safety goods of 5.09,[105] indicating that the WTA threshold (in the southwest quadrant) would be around €407,200 per QALY lost. So, apart from the question whether Dutch society would accept health loss at all, 3.5% better approaches the chance of MPVD being cost-effective at €80,000 willing to pay for an additional QALY than 11%.

Fig. 11: WTP/WTA disparity in the CE-plane

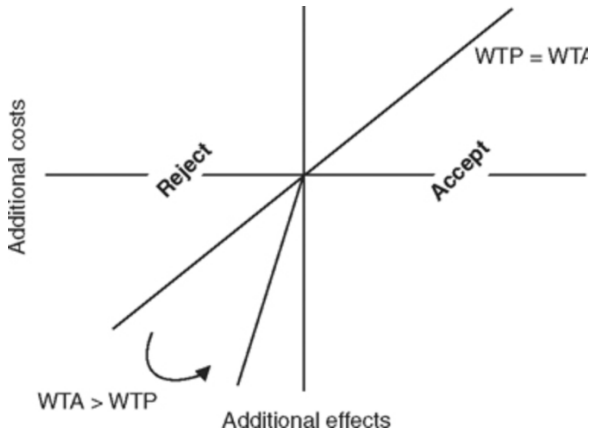

Figure reused from Severens *et al.*[106]

Cost-effectiveness analyses for orphan drugs

A criticist view on this cost-effectiveness analysis could challenge whether it is useful to conduct a classical cost-utility analysis for an orphan drug in the first place. In general, orphan drugs are hardly ever cost-effectiveness, despite significant gains in health effects, because of tremendously high costs concerned with the treatment.[107] Recouping R&D costs is but one goal of setting a certain price for daratumumab. The drug performs in an unprecedented manner in both advanced and untreated myeloma and has a favorable adverse events profile. Recently, in May 2018, the FDA has approved Darzalex® for the treatment of newly diagnosed myeloma in combination with MPV.[108] In the United States,

daratumumab has now licensed indications for practically every line of myeloma treatment. The total population of potential users has grown after CASTOR, POLLUX, EQUULEUS,[109] ALCYONE and refractory myeloma phase 1-2[110] trials. Now the question is whether Janssen-Cilag will decrease its price in the negotiations or pursue a marketing strategy in which the high price of daratumumab is maintained.

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Appendices

Appendix A1. Search strategies in PubMed/MEDLINE

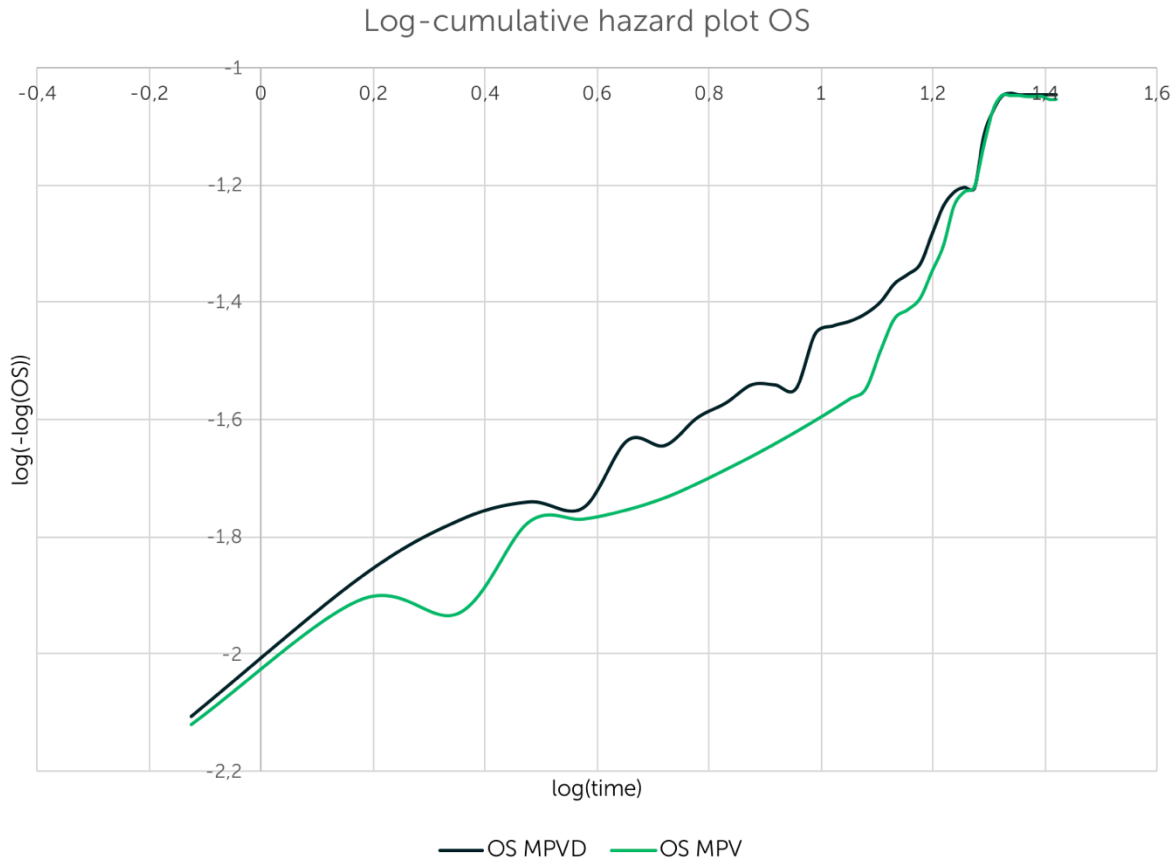
Utilities (2 February 2018)

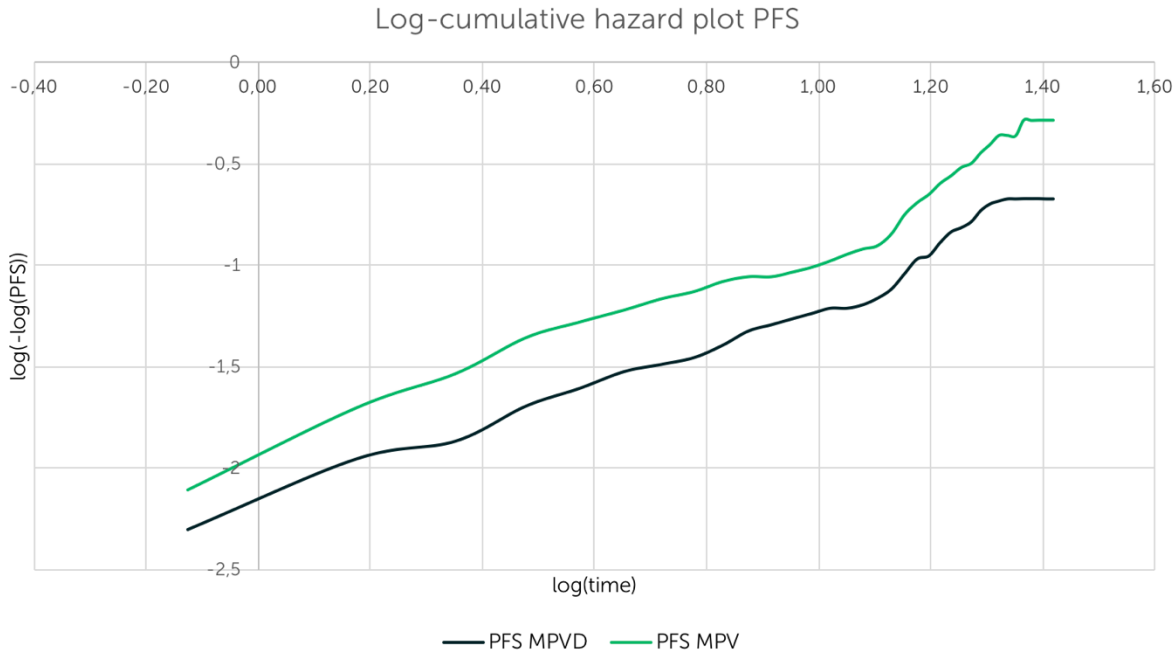
	Search strings			Hits
	utility	OR	(quality of life)	820
AND	"multiple myeloma"	OR	Kahler*	

Models for economic evaluations in MM (February 2013 to 26 January 2018)[21]

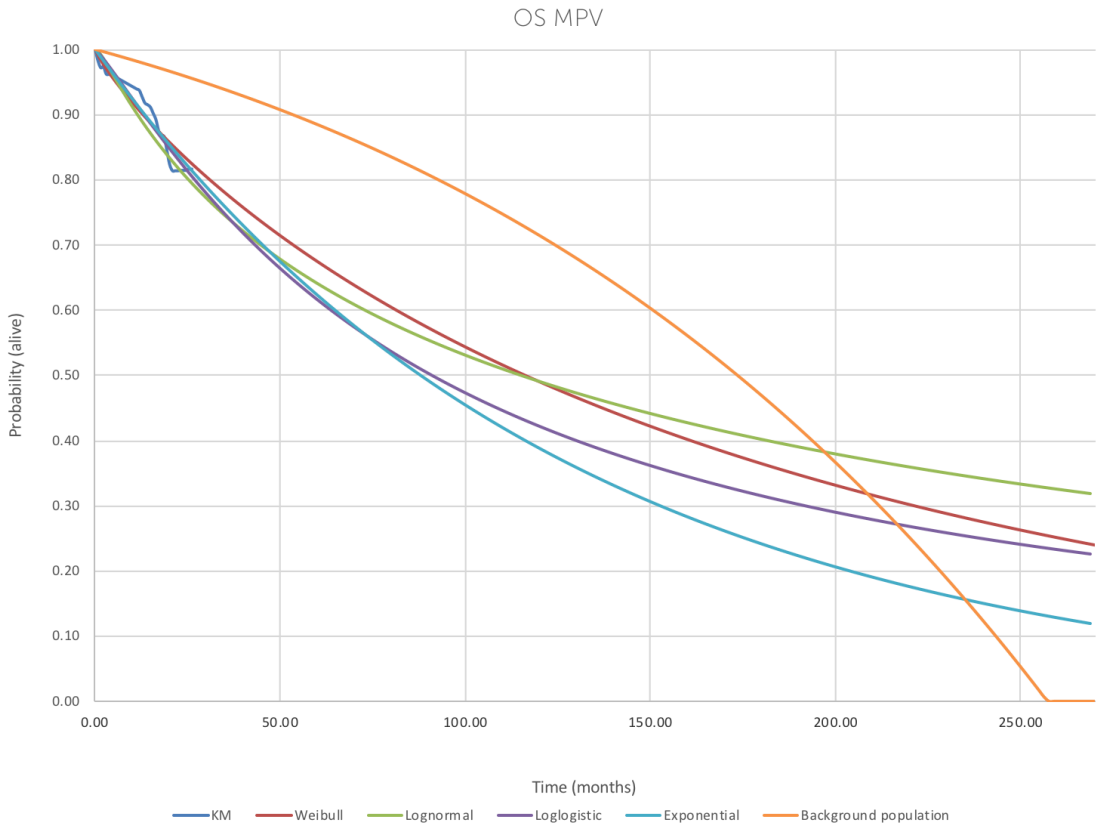
	Search strings							Hits
	Multiple myeloma	OR	myelomatosis	OR	plasma cell myeloma	OR	kahler* disease	
AND	(decision anal* OR decision analysis OR cost utility OR cost benefit OR cost mini*	OR	QALY OR quality adjusted life year* OR Markov OR Markov model* OR cost effectiveness	OR	cost-effectiveness OR decision model OR decision tree OR discrete event simulation OR DES	OR	transmission model OR area under the curve OR AUC OR survival partition model)	146

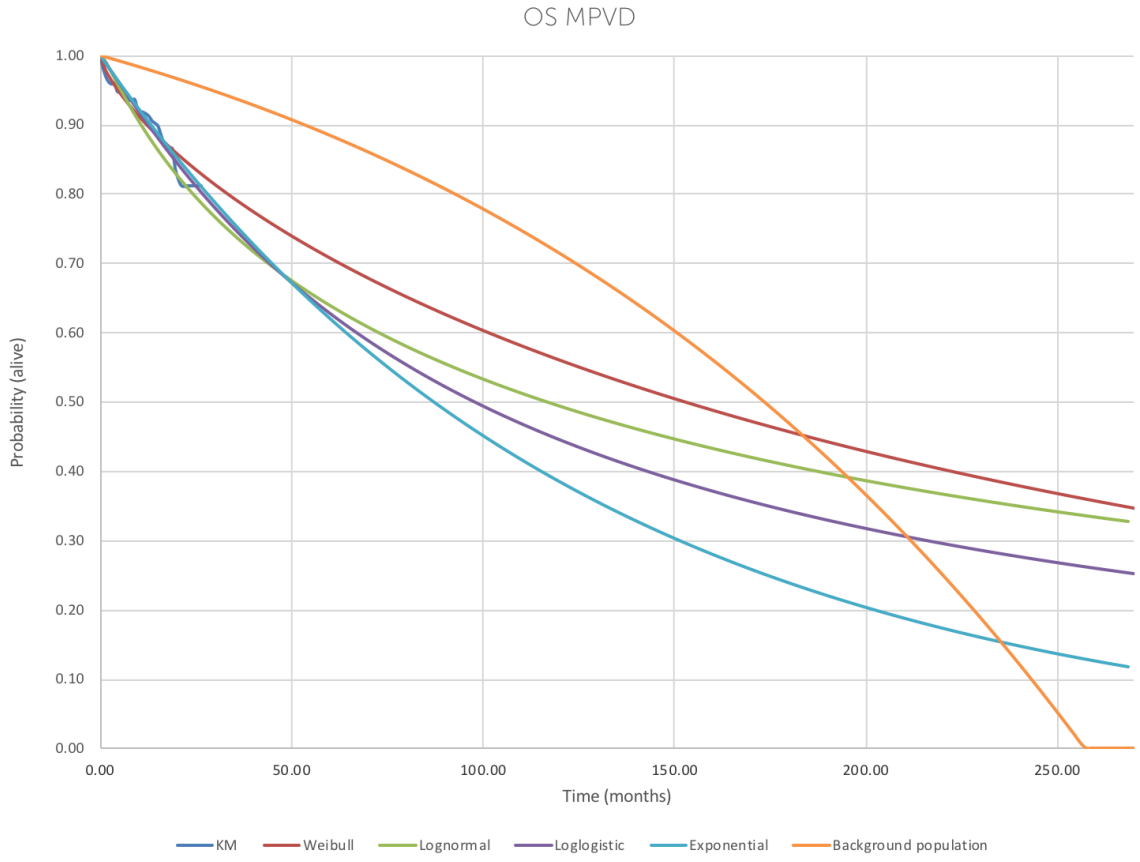
Appendix A2. Log-cumulative hazard plots OS and PFS first-line treatment

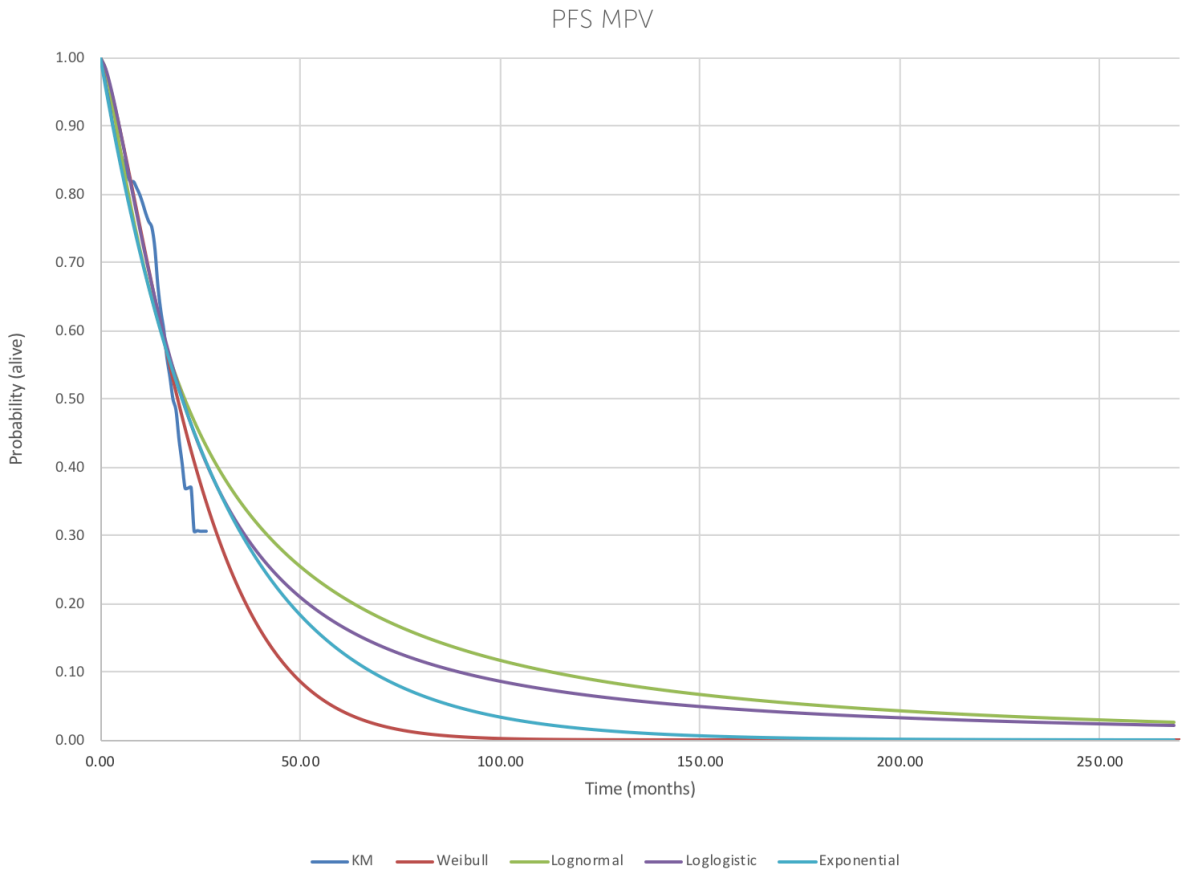


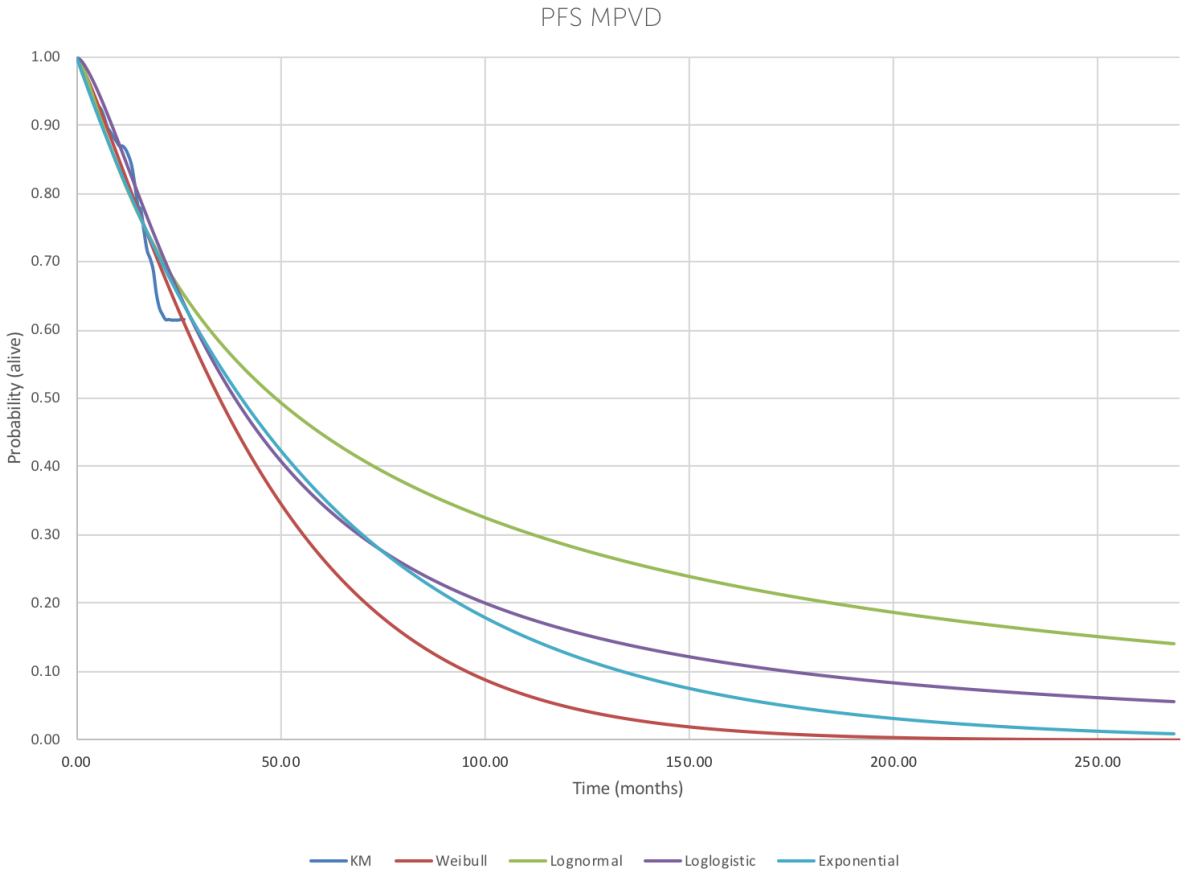


Appendix A3. Original Kaplan Meier curves and parametric distributions

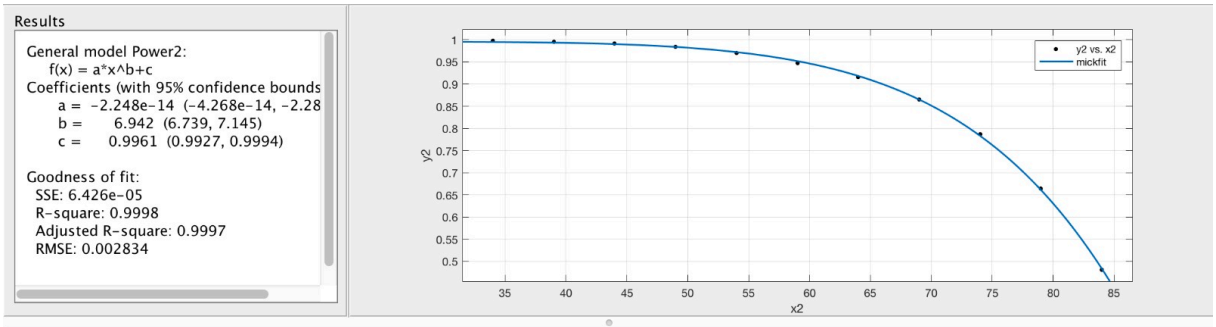





PFS MPV
Probability (alive)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
50.00
100.00
150.00
200.00
250.00
Time (months)
KM
Weibull
Lognormal
Loglogistic
Exponential

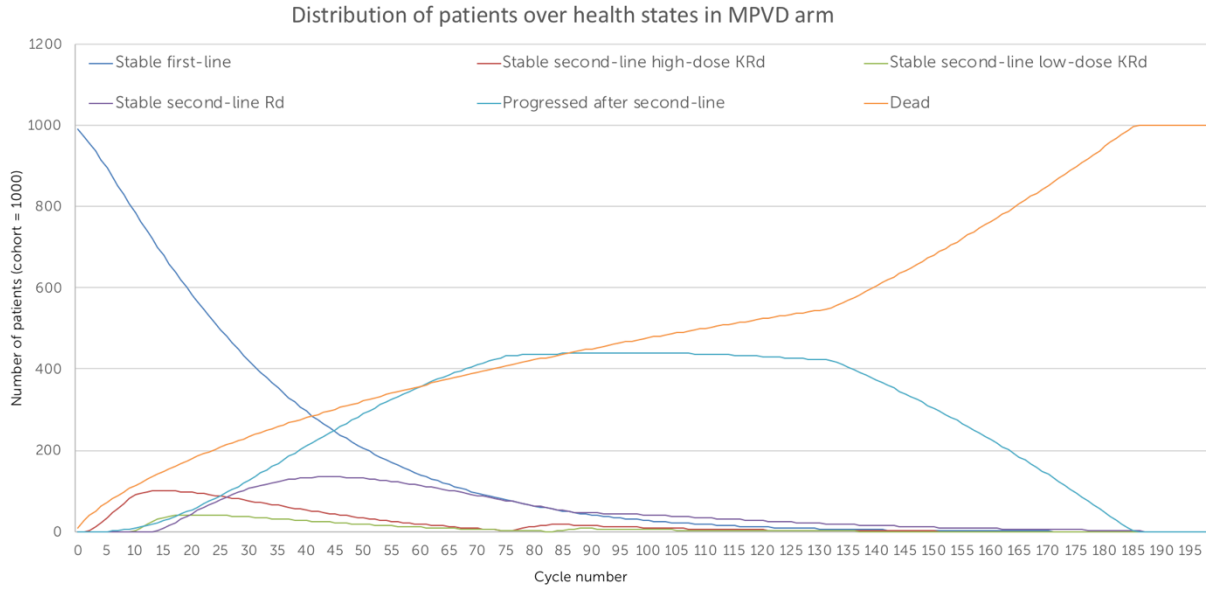

PFS MPVD
Probability (alive)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
50.00
100.00
150.00
200.00
250.00
Time (months)
KM
Weibull
Lognormal
Loglogistic
Exponential

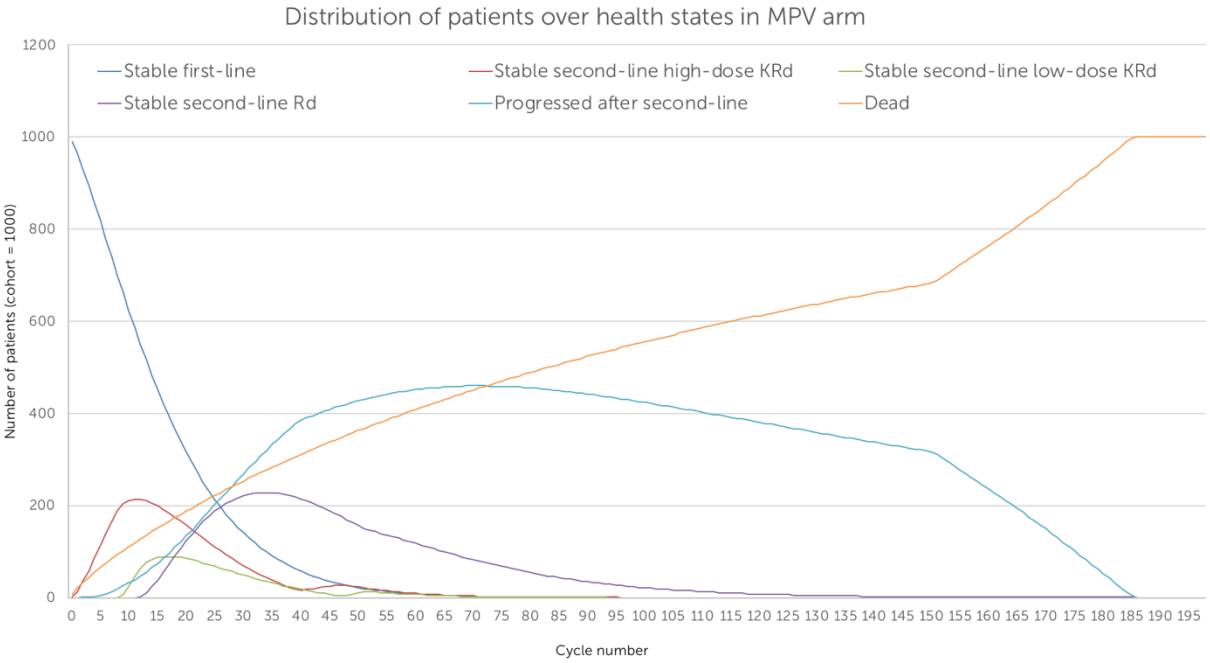
Appendix A4. MATLAB fit for survival function of general population



Age class specific probabilities of dying were retrieved from the WHO Life table for the Netherlands (data sampled in 2015). The chance of surviving throughout age class 70 to 74 years, for instance, was calculated as $1 - p(dying_{70\text{-}74})$. Eventually, all data points used for the curve fitting were calculated using the probability of surviving an age class multiplied with the probability of surviving the consequent age class, and so on. Finally, these data points were fitted to a power term equation using MATLAB. In the survival data extrapolation sheet, this equation was used to calculate the proportion of the background cohort (so, the general population) alive at any age above 71 years. From the age where the extrapolated OS exceeded the probability of being alive in the background population onwards, the latter value was taken for OS. The age at which the curves intersect is 92 years for both MPVD and MPV.

Appendix A5. Distribution of patients over health states





At cycles 75 (MPVD) and 45 (MPV) two small "bumps" can be observed for the states reflecting high- and low-dose KRd during second-line treatment. These bumps are the result of the fact that number of patients in second- and third/fourth-line treatment can only be estimated with Equations 3 and 4, but not calculated exactly. The cycles where the bumps occur reflect the time points where the model changes from one estimation method to another. Alternative approaches were tried – to prevent the bumps in the curves – but led to deviations from original cohort size (1,000) from cycles 75 and 45 onwards. The kinks in the orange curves (dead) reflect time points where OS is bound with general life expectancy.

Appendix A6 Fieller's theorem for calculation of confidence intervals

Confidence intervals (CIs) for ratios of means can be calculated using Fieller's theorem. Variance of incremental costs (ΔC) and effects (ΔE), and covariance of incremental costs and effects were retrieved from PSA results. With alpha set to 0.025 (two-sided), and the standard score retrieved from z-tables, upper and lower limits of CIs were calculated using the quadratic equation:

$$R^2[\Delta E^2 - z^2 var(\Delta E)] - 2R[\Delta E \cdot \Delta C - z^2 cov(\Delta E, \Delta C)] + [\Delta C^2 - z^2 var(\Delta C)] = 0$$

Followed by:

$$CI\ bounds = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

CI bounds could not be reached for the main mean probabilistic ICER, since the discriminant was equal to $-3.30 \cdot 10^{11}$, hence the quadratic function could not be solved for R. Therefore, alternatively the number of PSA simulations below the WTPT of €80,000 per QALY gained was provided as an indicator of uncertainty around the main mean probabilistic ICER.

Inner loop

```
Sub EVPPI()

Sheets("Analysis").Select
    Range("E7").Select
    ActiveCell.FormulaR1C1 = "1"
    Application.DisplayStatusBar = True
    Index = 0
    Trials = 50

Do

Sheets("VOI").Select
Range("I4") = ThisWorkbook.Sheets("VOI").Cells(4, "R").Value
Range("I5") = ThisWorkbook.Sheets("VOI").Cells(5, "R").Value
Range("I6") = ThisWorkbook.Sheets("VOI").Cells(6, "R").Value

Simulation

Sheets("Simulation").Select
ActiveWindow.ScrollWorkbookTabs Position:=xlLast
    Range("V11:W11").Select
    Selection.Copy
    Sheets("VOI").Select
    Range("F11:G11").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:=
_
        False, Transpose:=False

Index = Index + 1

Loop While Index < Trials


End Sub
```

Outer loop

```
Sub outer()

Sheets("Analysis").Select
Range("E7").Select
ActiveCell.FormulaR1C1 = "1"
Application.DisplayStatusBar = True
Index = 0
Trials = 50

Do

EVPPI

Sheets("VOI").Select
ActiveWindow.ScrollWorkbookTabs Position:=xlLast
    Range("F9:G9").Select
```

```
    Selection.Copy
    Range("I11:J11").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone,
SkipBlanks:= _
        False, Transpose:=False

Index = Index + 1
Application.StatusBar = "Simulation " & Index & " of 50 trials"

Loop While Index < Trials

End Sub
```

Appendix B1. Disutilities

Adverse event	Disutility	SE	Distribution (PSA)	Duration (days)	Source
Neutropenia	0.145	10%	Gamma	13.2	[28]
Anemia	0.31	10%	Gamma	180	[25]
Thrombocytopenia	0.31	10%	Gamma	14.1	[25]
Peripheral sensory neuropathy	0.65	10%	Gamma	180	[25]
Diarrhoea	0.103	10%	Gamma	12	[28]
Pyrexia	0.15	10%	Gamma	9.4	[28]
Nausea	0.103	10%	Gamma	24.3	[28]
Pneumonia	0.14	10%	Gamma	12	[28]
Infusion-related reaction	0.098	10%	Gamma	5	[111]
Fatigue	0.11	10%	Gamma	14.6	[13]
Hypokalemia	0.0	10%	Gamma	11.4	[28] (analogy with hypophosphatemia)
Dyspnea	0.05	10%	Gamma	11	[112,113]
Hypertension	0.0	10%	Gamma	28	[28]
Acute renal failure	0.11	10%	Gamma	29.8	[28]
Cardiac failure	0.063	10%	Gamma	180	[28]
Ischaemic heart disease	0.05	10%	Gamma	180	Expert opinion: slightly smaller decrement than cardiac failure

Appendix B2. Medication-related resource use and costs

CPIs and PPPs

Index	From	To	Factor
CPI (NL)	2014	2018	1.0385
CPI (NL)	2015	2018	1.0323
PPP (2015)	France	NL	1.0012

Medication (treatment schemes)

Treatment line	Arm	Drug	Dose	Frequency			Dose intensity (SE=10% of mean, normal distribution in PSA)
First-line MPV(D) (treatment cycle = 6 weeks)	MPV arm			cycle 1	cycles 2-9		
		Bortezomib	1.3 mg/m2 s.c.	2x /week, week 1,2,4,5	1x week, week 1,2,4,5		96,15%
		Melphalan	9 mg/m2 p.o.	1x/day, days 1,2,3,4	1x/day, days 1,2,3,4		97,22%
		Prednisone	60 mg/m2 p.o.	1x/day, days 1,2,3,4	1x/day, days 1,2,3,4		98,88%
	MPVD arm			cycle 1	cycles 2-9	until progression	
		Bortezomib	1.3 mg/m2 s.c.	2x /week, week 1,2,4,5	1x/week, week 1,2,4,5		96,15%
		Melphalan	9 mg/m2 p.o.	1x/day, days 1,2,3,4	1x/day, days 1,2,3,4		97,22%
		Prednisone	60 mg/m2 p.o.	1x/day, days 2,3,4	1x/day, days 2,3,4		104,92%
		Dexamethasone	20 mg p.o.	1x/day, day 1 + 1x/week, weeks 1,2,3,4,5,6	1x/day, day 1 + 1x/3 weeks, weeks 1,4	1x/ 4 weeks	104,92%
		Daratumumab	16 mg/kg i.v.	1x/week, weeks 1,2,3,4,5,6	1x/3 weeks, weeks 1,4	1x/ 4 weeks	99,69% / 100% / 66,67%
		Montelukast	10 mg p.o.	1st infusion, ±25% before every infusion	±25% before every infusion	±25% every infusion	
		Tavegil	2 mg i.v.	before every infusion	before every infusion	before every infusion	
Second-line Rd+carfilzomib	All patients			cycles 1-12	cycle 13-18	until progression	

(treatment cycle = 4 weeks)							
		Lenalidomide Dexamethasone Carfilzomib	25 mg p.o. 20 mg p.o. 27 mg/kg i.v.	day 1-21 2x/week, weeks 1,3 2x/week, weeks 1,2,3	day 1-21 2x/week, weeks 1,3 2x/week, weeks 1,3	day 1-21 2x/week, weeks 1,3	
Supportive medication	All patients, all lines						
		Zoledronic acid Calcium/vitamin D (Calci Chew) Acyclovir Ascal cardio	3-4 mg i.v. 500 mg/400 IE p.o. 800 mg p.o. 100 mg p.o.	1x/4 weeks daily daily during bortezomib daily during lenalidomide			
Third- and fourth-line treatment (only dara)	MPV arm	Daratumumab Montelukast Tavegil	16 mg/kg i.v. 10 mg p.o. 2 mg i.v.	2.25x per cycle 2.25x per cycle 2.25x per cycle			

Medication (drug prices)

Drug	Relevant unit(s)	Unit cost (€, 2018, NL)	Source
Bortezomib	Flacon 3.5 mg	1156.05	www.medicijnkosten.nl
Melphalan	Pill 2 mg	2.51	
Daratumumab	Vial 5 ml (=100 mg) or 20 ml (=400 mg)	483.36 / 1933.44	
Prednisone	Pill 5 mg	0.05	
Dexamethasone	Pill 20 mg	0.89	
Montelukast	Pill 10 mg	0.04	
Tavegil (clemastine)	Vial 2 ml (=2 mg)	0.74	
Lenalidomide	Pill 25 mg	290.98	
Carfilzomib	Powder for infusion 10, 30 , 60 mg	212, 636, 1272	
Zoledronic acid	Infusion bag 100 ml (=4 mg)	168.85	
Calcium [carbonate] /vitamin D (Calci Chew)	Pill 500/400	0.12	
Acyclovir	Pill 800 mg	0.64	
Ascal cardio	Pill 100 mg	0.06	

Drug administration costs (intravenous and subcutaneous medication only)

Drug	Administriation mode	Price (€)	Price year (country)	Price inflated to 2018 (€)	SE	Distribution (PSA)	Frequency	Source
Daratumumab	Clinical (admission)*	3400	2007 (NL)	4674.05	206.41	Gamma	25%	[48]
	Outpatient	305	2007 (NL)	356.71	18.93	Gamma	75%	[48]
Bortezomib	home	158.80	2015 (France)	161.70	20%	Gamma	0%	[50]
	clinical	3400	2007 (NL)	4674.05	206.41	Gamma	25%	[48]
	outpatient	305	2007(NL)	893.11	18.93	Gamma	75%	[48]
Carfilzomib	Clinical	3400	2007 (NL)	4674.05	206.41	Gamma	25%	[48]
	Outpatient	305	2007 (NL)	356.71	18.93	Gamma	75%	[48]
** Duration of an admission is assumed to be 5 days*								

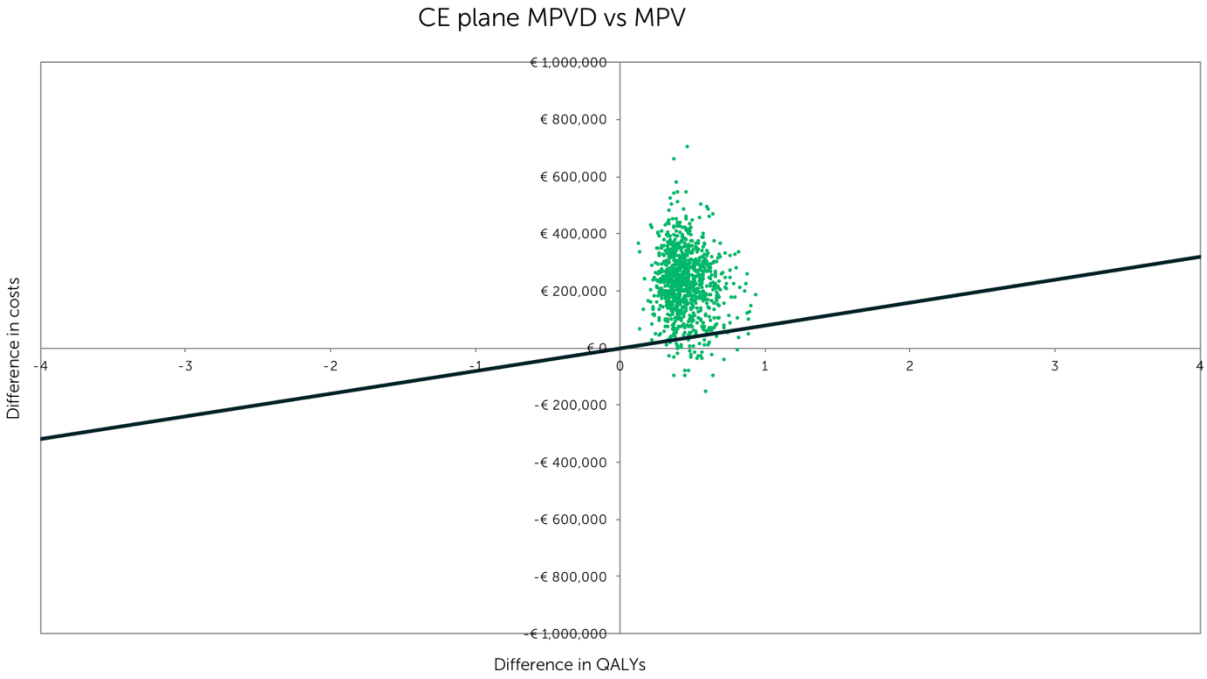
Other resources used

Resource item	Monthly price (€)	Price year (country)	Price per cycle inflated to 2018 (€)	Price per cycle (MSc thesis M. de Weerd) (€)	Price per cycle in model (€)	SE	Distribution in PSA	Source
POM-DEX	9,294	2015 (France)	14,411	15,235	15,235	20%	Gamma	[54,58]
BOR-DEX	4,744	2015 (France)	7,356	Not available	7,356	20%	Gamma	[54]
Rd/REP	3,817	2015 (France)	5,919	9,581	9,581	20%	Gamma	[54,58]
Daratumumab (including Montelukast and Tavegil)	9,776	2018 (NL)	14,664	14,227	14,664	20%	Gamma	[58,71]
Other resource costs (fixed for all lines of treatment and regimens)	2,139	2015 (NL)	3,317	N/A	3,317	20%	Gamma	[53]

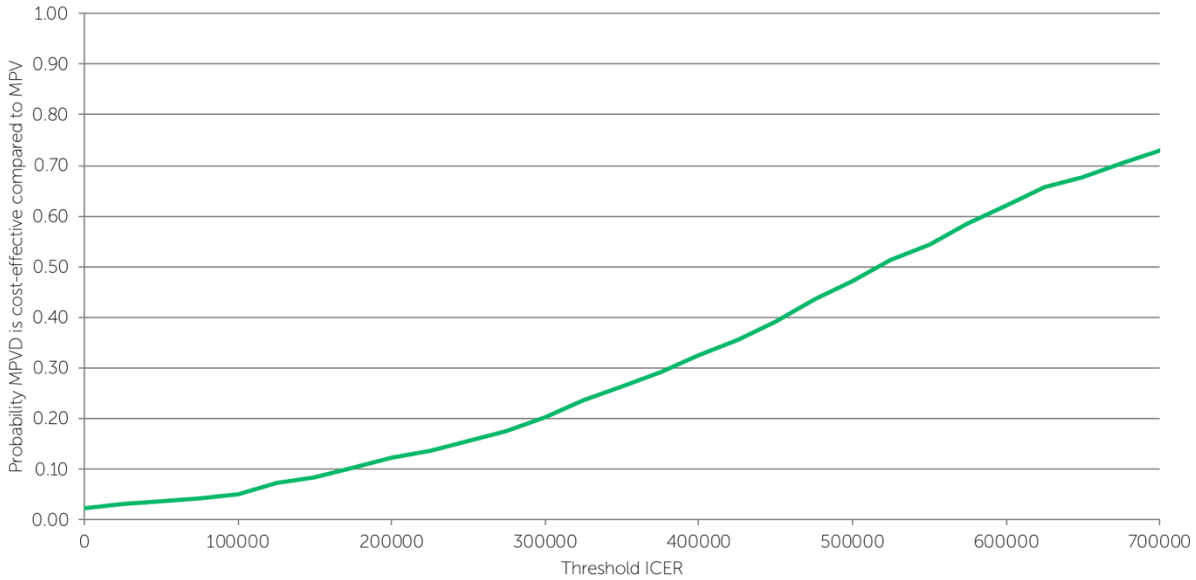
Appendix B3. Future medical costs (PAID tool version 1.1)

Age	Healthcare costs unrelated to MM for last year of life, inflated to 2018 (€)	Healthcare costs unrelated to MM for other years of life, inflated to 2018 (€)
70	45,997.39	6,506.22
71	46,620.97	6,846.58
72	47,254.05	7,220.70
73	47,859.74	7,630.56
74	48,421.13	8,079.19
75	48,923.29	8,569.75
76	49,358.00	9,105.74
77	49,697.31	9,690.45
78	49,926.71	10,326.04
79	50,054.65	11,017.07
80	50,090.52	11,772.08
81	50,116.42	12,602.00
82	50,182.66	13,518.69
83	50,388.77	14,559.28
84	50,995.10	15,781.02
85	52,271.25	17,228.44
86	54,309.28	18,973.03
87	57,160.32	21,075.88
88	60,780.20	23,559.39
89	65,138.06	26,449.87
90	70,095.91	29,730.85
91	75,245.07	33,274.00
92	80,134.48	36,932.84
93	84,424.58	40,625.98
94	88,031.20	44,421.77
95	90,978.51	48,469.91
96	93,017.63	53,124.07
97	93,717.01	58,727.09
98	92,713.65	65,516.64
99	90,207.05	74,146.82

Appendix B4. CE-plane and CEAC for joint modelling approach



a. CE-plane for the joint modelling approach. The line in dark green represents the societal WTP threshold (€80,000 per QALY gained)



b. CEAC for the joint modelling approach.

Appendix C1. List of assumptions

No.	Assumption	Justification with supporting literature
1	No age- or comorbidity-related dosage adjustment for medication, except for dexamethasone (standard 20 mg), whilst percentages of intended maximum dosage are respected.	Dosage adjustment was not mentioned in the ALCYONE trial;[12] it is assumed that dosage adjustments made are captured in the "percentage of intended dosage administered". Moreover, the IMWG is of the opinion that bortezomib can be administered safely without dosage-adjustment in impaired renal function, which is often present in MM patients.[114] The Dutch treatment guideline provides bortezomib dosage adjustment tables for the elderly, but dosage adjustment is based on individual frailty scores that are not available to this analysis.
2	Supportive treatment for prevention of skeleton-related complications is based on International Myeloma Working Group Consensus Statement.	Recommendations in the Dutch treatment guideline are scarce; the IMWG Statement is referred to.[114]
3	G-CSF is not included in standard medication. It is assumed that the costs of G-CSF administered in case of neutropenia are included in the lump sum of neutrophil-related adverse event costs.	Granulocyte colony stimulating factor (G-CSF = Filgrastim) is not generally administered to patients ineligible for ASCT, unless they suffer from grade 4 lenalidomide-induced neutropenia or under special circumstances of grade 2/3 neutropenia.[11]
4	a. Bortezomib is not administered at home; only in the hospital. b. If concomitant administration of different drugs in a scheme is possible (e.g., daratumumab and bortezomib), administration costs are charged once.	Home administration of subcutaneous bortezomib is only performed in experimental settings; a deterministic scenario analysis was performed to assess the effect on cost-effectiveness if bortezomib is self-administered by patients at home (see results). Administration costs are a combination of staff costs (haematology nurses who prepare and administer the infusion, but also haematologist costs for monitoring laboratory parameters prior to infusion), and pharmacy costs.[13] Marginal preparation costs for a second or third drug to be administered simultaneously with the first are relatively low. Costs would be overestimated if administration costs were charged twice in case of concomitant administration of two drugs.
5	a. Standard monitoring tests consist of complete blood count and biochemistry (CRAB). Frequency of testing is as follows: - During first-line treatment: prior to every administration; - After first-line treatment (stable): once per four weeks; - During second-line treatment: prior to every	The most appropriate combination of diagnostic tests to monitor disease stability and treatment response is a topic of debate. Based on empirical evidence of relapse and disease progression patterns, it can be justified to only assess basic lab (biochemistry [providing information on CRAB criteria] and complete blood count) on a very regular basis. If immunoglobulin tests are performed every cycle, other diagnostics can be saved for cases in which there is a clear clinical indication,[72,115] particularly since 98% of patients with progression of disease were detected with routine immunoglobulin assessment (at least in post-transplant patients).[115]

	administration, which is on average 7 times per cycle.	
	b. Serologic tests (IgA, IgM, IgG blood level assessment in blood and urine) and protein electrophoresis are performed prior to every treatment cycle, and once per three months in stable disease after first-line treatment.	During follow-up of minimal residual disease, full blood count and CRAB assessment is recommended once per two to three months.[66]
	c. Cytology (bone marrow aspiration) and Whole-body PET/CT are performed prior to every fourth treatment cycle to assess treatment response. Cytology and Whole-Body PET/CT are also performed at progression from first- to second- or from second- to third-line therapy.	According to IMWG response criteria, cytology material should be harvested once per three to four cycles to assess treatment response, and in case progression is suspected.[45] Imaging (currently still PET/CT) should be performed as frequent as cytology.[45]
	d. MRI utilization for evaluation of spinal cord compression is not taken into account.	Although the indication area of MRI is expanding, it is yet only recommended by indication, especially if lytic bone lesions with spinal cord compression are suspected.[66] Approximately 5% of MM patients will develop spinal cord compression,[116] with increased risks at more advanced stages of MM. In approximately 60% of patients with suspected spinal cord compression the diagnosis was actually established.[117] Hence, the frequency of MRI per patient per cycle is very low, so MRI utilization is not taken into account.
6	There is no place for consequent daratumumab-containing regimens after first-line daratumumab application.	Daratumumab is administered until progression or major adverse events which demand cessation of daratumumab administration in the ALCYONE trial;[12] this may imply that efficacy of daratumumab post-progression is not expected in this particular case.
7	Dosage adjustment for carfilzomib in the first two administrations of the first cycle is not taken into account.	The recommended dosage adjustment of 20 mg/kg instead of 27 mg/kg in the first two administration of cycle 1 is barely expected to influence total treatment costs, especially incremental costs. For simplification, this is not taken into account in the model.

Appendix C2. List of abbreviations

AIC	Akaike information criterion
ALCYONE	RCT testing MPVD vs MPV in untreated MM
ASCT	Autologous stem cell transplantation
ASPIRE	RCT testing KRd vs Rd in relapsed MM
BIC	Bayesian information criterion
BSA	Body surface area
CASTOR	RCT testing VdD vs Vd in MM after at least one prior line of therapy
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CPI	Consumer price index
CRAB	Calcium, renal failure, anaemia, bone lesions
CUA	Cost-utility analysis
DARA	Daratumumab (Darzalex®)
DSA	Deterministic sensitivity analysis
EQUULEUS	Open-label, non-randomized trial testing POM-DEX plus DARA in relapsed MM
ESHPM	Erasmus School of Health Policy and Management
EVPI	Expected value of perfect information
EVPPI	Expected value of partial perfect information
HOVON	Dutch Foundation for Adult Haemato-Oncology
HR	Hazard ratio
HTA	Health technology assessment
HR-QoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
KRd	Kyprolis® (carfilzomib), Revlimid® (lenalidomide), dexamethasone
MM	Multiple myeloma
MPV	Melphalan, prednisone, Velcade® (bortezomib)
MPVD	Melphalan, prednisone, Velcade® (bortezomib), Darzalex® (daratumumab)
MRI	Magnetic resonance imaging
OS	Overall survival
PET/CT	Positron emission tomography/computed tomography
PEVPI	Population-based expected value of perfect information
PFS	Progression-free survival
POLLUX	RCT testing RdD vs Rd in MM after at least one prior line of therapy
POM-DEX	Pomalidomide, dexamethasone

PPP	Purchasing power parity
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
Rd	Revlimid® (lenalidomide), dexamethasone
REP	Revlimid® (lenalidomide), Endoxan® (cyclophosphamide), prednisone
RR	Relative risk
SE	Standard error
SD	Standard deviation
VOI	Value of information
VTE	Venous thromboembolism
WTA(T)	Willingness-to-accept (threshold)
WTP(T)	Willingness-to-pay (threshold)