【ダラキューロ配合皮下注】に関する費用対効果評価

[第 1.0 版]

【ヤンセンファーマ株式会社】
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【目次】

0．要旨

In the table below, include the content for the 主要分析. For other analysis performed, details can be found in the report section 5.3.

分析対象技術名 [1.1 節]	ダラキューロ配合皮下注（ダラツムマブ・ボルヒアルロニダーゼアルファ）(Dara SC)
他国の医療技術評価機関における評価結果 [1.8 節]	イギリス（NICE）：その他* イギリス（SMC）：推奨 (Reimbursed in previously recommended regimens for Dara IV) フランス（HAS）：SMR-important、ASMR-V（効率性評価：不要） ドイツ（IQWiG）：その他* カナダ（CADTH）：その他* オーストラリア（PBAC）：推奨（Based on a cost minimization basis with Dara IV.） *NO HTA EVALUATION required for formulation changes. Reimbursement based on Dara IV
対象とする疾患・集団 [2.1 節]	造血幹細胞移植の適応とならない未治療の多発性骨髄腫及び再発又は難治性の多発性骨髄腫
比較対照技術名 [2.2 節]	ダラザレックス点滴静注 (Dara IV)
分析の立場と費用の範囲 [2.3 節]	公的医療の立場 公的医療費
使用する効果指標 [2.4 節]	費用最小化分析：なし（費用のみ）
設定した分析期間 [2.5 節]	費用最小化分析：32 週間（主要評価）および 1 年（感度分析）
割引率 [2.6 節]	費用最小化分析：なし (分析期間 ≤ 1 年)
システマティックレビューのクリニカルクエスチョン [3.1/3.3 節]	P: 造血幹細胞移植の適応とならない未治療の多発性骨髄腫及び再発又は難治性の多発性骨髄腫 I: Dara SC C: Dara IV O: 有効性（ORR、PFS、OS）、安全性、HRQoL
システマティックレビュー結果の概要 [3.2/3.4 節]	システマティックレビューの結果、組み入れ対象となる臨床試験等は 1 件であった。
間接比較の結果 [3.7 節]	該当せず

追加的有用性の有無　[3.8 節]	□ 追加的有用性あり ■「追加的有用性なし」あるいは「あるとは判断できない」 有効性（ORR 及び PFS）に関して Dara SC は Dara IV に対して非劣性であることが示された。また Dara SC と Dara IV の間で Infusion related reaction（AE）率及び治療満足度に差があることが確認されているが、これらのベネフィットを費用効用分析の枠組みに組み込むことは困難である。治療満足度が高いことに加えて、薬物投与期間が短く、患者の拘束時間は短い。さらに、Dara SC は医療従事者による医療行為に要する時間を大幅に短縮し、患者管理全体の効率を改善する可能性がある。よって、その他の分析として、薬剤投与のための来院時に HCP に要する時間とそれを金銭的価値に換算した値の分析を実施した。: [その他：HCP の時間的観点からの費用差]
費用対効果の分析方法の概要 [4.1.1 項、4.2 節等]	Based on the additional benefit assessment result, Janssen determined to take a conservative approach and performed a cost minimization analysis as below. An Excel model was built to calculate weekly direct medical cost including drug, drug administration, hospitalization and IRR (AE) management. Three daratumumab regimens were included, DVMP, DRd and DVd. For each of the regimen, we compare the accumulative direct medical cost between Dara SC (intervention) and DARA IV (comparator). Final results were pooled by the percentage of usage of each regimen in actual clinical practice based on MDV data. The duration comparison is set to be 32 weeks based on average daratumumab treatment duration in Japan as base case. A sensitivity analysis was performed with the duration of 52 weeks [Sensitivity analysis 1]. Another sensitivity analysis was performed assuming [redacted] of patients receiving DARA SC regimen (due to the improved

	administration and safety) will not require hospitalization for regimen initiation [Sensitivity analysis 2].
結果の概要 [5.1 節]	Dara SC results in lower total cost compared with Dara IV. Compared with Dara IV, Dara SC reduced total direct medical costs by ¥546,091 in the base case. The cost saving ranged from ¥443,078 to ¥721,951 among different regimens. The sensitivity analysis showed consistent results. In Sensitivity analysis 1 and 2, Dara SC reduced total direct medical costs by ¥550,036 and ¥481,985, respectively.
ICER の所属する確率が最も高いと考える区間	In the base case analysis and sensitivity analysis of the main analysis, the result all demonstrated cost saving. Two other analysis results provided the additional evaluation on HCP time/cost saving that contribute to overall health care system efficiency and the ICER result in a subset of Multiple Myeloma patients (RRMM) comparing to different comparators. As it is agreed that the main evaluation focuses on different population, comparator, and/or perspective, the analyses only served as supplementary analyses.

1．対象となる医薬品･医療機器の性質

1.1 名称

- 製品名

  ダラキューロ配合皮下注

- 一般名

  ダラツムマブ（遺伝子組換え）1800mg、ボルヒアルロニダーゼ　アルファ（遺伝子組換え）30000 単位（1 バイアル 15mL 中）

1.2 保険償還価格

保険償還価格:	15mL 1 バイアル 434,209 円
算定方式:	類似薬効比較方式(I)
算定上の最類似技術	ダラザレックス点滴静注 400mg
有用性系加算	有用性加算 II
加算率	5%

1.3 治療効果のメカニズム

1.3.1 ダラツムマブ

ダラツムマブは，骨髄腫細胞に高発現する CD38 に特異的に結合し，直接的な作用及び免疫調節作用により高い抗腫瘍効果を示す。

1.3.2 ボルヒアルロニダーゼ アルファ

ボルヒアルロニダーゼ アルファは，皮下間隙における細胞外マトリックスの構成成分の一つであるヒアルロン酸を加水分解することでヒアルロン酸を脱重合し、細胞外マトリックスの粘性を一過性に低下させる。これにより、治療薬の拡散と吸収を促進する。

1.4 対象疾患

- 保険適用となる疾患

  多発性骨髄腫 (本分析の対象とする疾患)

  全身性 AL アミロイドーシス

- 分析対象とする疾患の疫学的性質(有病率、新規発症者数、好発年齢等)

日本における多発性骨髄腫(MM)の年間の発症率は 10 万人あたり約 6 人と推定され、2018 年の罹患推定値は 7,765 人である[1]。日本骨髄腫学会（旧 日本骨髄腫研究会）に属する施設を対象にした調査研究によると，2001～2012 年に診療された MM の初診時年齢の中央値は 67 歳である[2]。

CancerMpact により予測される将来の MM の 5 年有病者数の推移は以下のとおりである。5 年有病者数は過去 5 年以内に MM と診断された患者数のうち，推計対象年に生存している患

者数を示しており，5 年有病者数の推移から MM 全体における患者数の増減が予測される。MM 有病者数は今後も高齢人口の増加とともに緩徐に増加していくと考えられるものの，MM 患者は毎年一定の患者が亡くなってしまうため，急激な増加は予測されていない[3]。

- 表 1-1 MM*の 5 年有病者数

2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*ICD10のC90（多発性骨髄腫及び悪性形質細胞性新生物）のみ

- 分析対象とする疾患における当該医薬品･医療機器の使用(見込)者数

保険償還時の使用見込み数は、ピーク時市場規模予測で 6900 名である。

- 当該医薬品･医療機器を使用する患者の主な年齢(層)や性別等

国内の MM 患者集団は初診時年齢の中央値は 67 歳と比較的高齢者が多く、男性の割合がやや高いことが知られており[2]、ダラキューロ配合皮下注(Dara SC)の投与対象として想定される集団も国内の MM 患者集団と年齢層および性別において同様である。

実際に、再発又は難治性の多発性骨髄腫(RRMM)患者を対象としたダラザレックス点滴静注(Dara IV)の製造販売後特定使用成績調査[4]によると、安全性解析対象症例の患者背景は、男性が [redacted]%（[redacted] 例）、女性が [redacted]%（[redacted] 例）であった。年齢の中央値は [redacted] 歳、平均値 [redacted] 歳（範囲:[redacted] 歳）であり、65 歳未満が [redacted]%（[redacted] 例）であった。

1.5 使用方法等

本剤の使用方法を以下の表に示す。

- 表 1-2 本剤の使用方法

投与経路	皮下投与
投与方法	他の抗悪性腫瘍剤との併用
1 回あたりの投与量	ダラツムマブ（遺伝子組換え）として 1,800mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え）30,000 単位（2,000 単位/mL））
投与頻度	以下の A 法又は B 法の投与間隔で皮下投与する。 A 法：1 週間間隔、2 週間間隔及び 4 週間間隔の順で投与する。 B 法：1 週間間隔、3 週間間隔及び 4 週間間隔の順で投与する。
平均的な投与期間	疾患増悪まで継続的に使用

1.6 対象疾患の治療における当該医薬品･の位置づけ

ダラツムマブは MM 治療における有用な薬剤であり、造血幹細胞移植の適応とならない未治療の MM(TIE NDMM)患者及び RRMM 患者に対して，国内外の診療ガイドラインで推奨されている。特に国内の日本血液学会及び日本骨髄腫学会の診療ガイドラインにおいて，ダラツムマブは TIE NDMM 患者に対する推奨治療レジメンすべてに含まれている唯一の薬剤である。

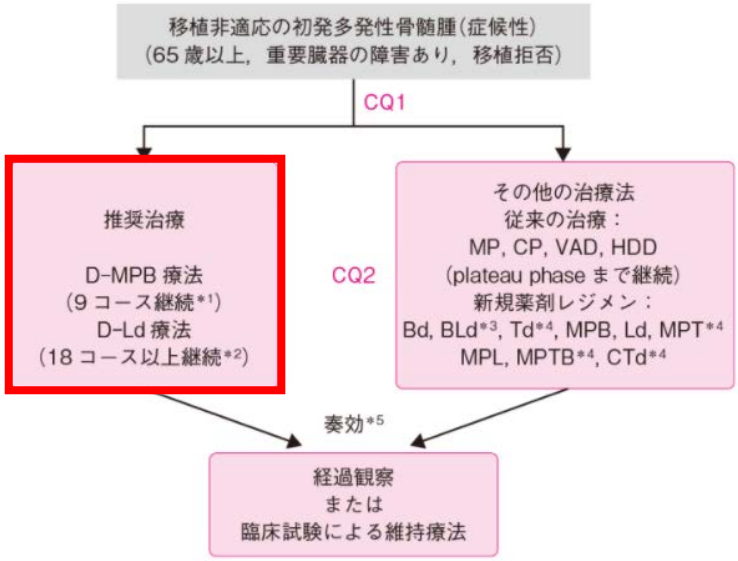
また NCCN ガイドラインでは，本剤は，すべてのダラツムマブ治療レジメンにおいて Dara IV と併記されている。国内ガイドラインにおいても，有効性を維持しつつ利便性と安全性を大きく改善する本剤は Dara IV と同様に推奨されることが想定される。

TIE NDMM 患者及び RRMM 患者の治療における国内及び海外のガイドラインの推奨は以下のとおりである。

1.6.1 国内ガイドライン（日本血液学会）

➢ 造血器腫瘍ガイドライン 2018 年版補訂版 第Ⅲ章 骨髄腫より抜粋

移植非適応の初発 MM の治療アルゴリズム



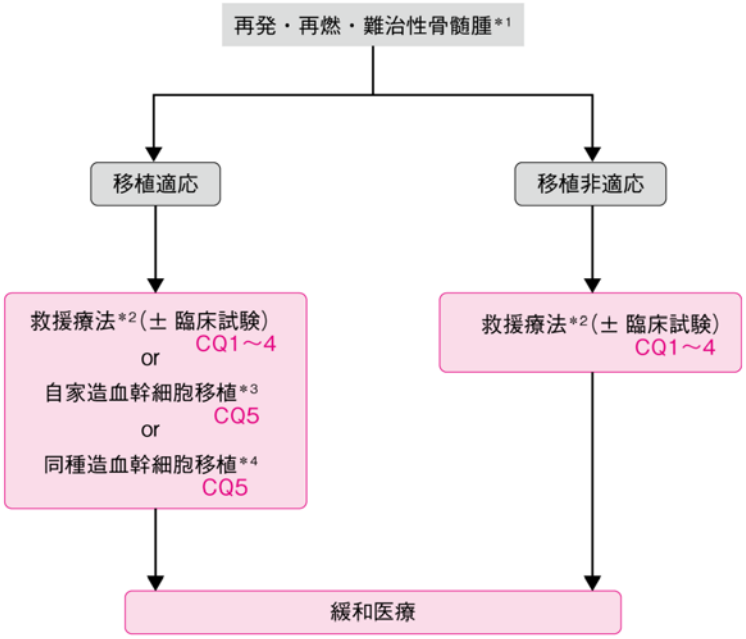
【移植非適応の初発多発性骨髄腫（症候性）】

CQ1 移植非適応の多発性骨髄腫（症候性）に対する推奨治療レジメンは何か

推奨グレード：カテゴリー1

新規薬剤を用いた D-MPB 療法（ダラツムマブ，メルファラン，プレドニゾロン，ボルテゾミブ）もしくは，D-Ld 療法（ダラツムマブ，レナリドミド，少量デキサメタゾン）が推奨される。

RRMM の治療アルゴリズム



【再発・難治性骨髄腫】

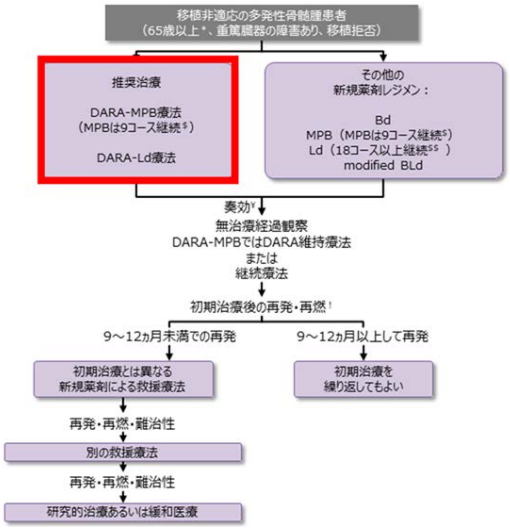
CQ1 再発・難治性骨髄腫患者に対する新規薬剤療法は大量デキサメタゾン療法に比べて生存期間を延長させるか

推奨グレード：カテゴリー1

再発・難治性骨髄腫患者に対する新規薬剤療法は，大量デキサメタゾン療法と比較し，無増悪生存期間や生存期間を延長させるので推奨される。

1.6.2 国内ガイドライン（日本骨髄腫学会）

➢ 多発性骨髄腫の診療指針 第 5 版より抜粋



BLd：BOR+lenalidomide(LEN)+少量DEX、DARA-MPB：少量daratumumab(DARA)+L-PAM(MEL)+prednisolone(PSL)+BOR、LDH：lactate dehydrogenase

¥ 初回導入療法にて非奏功の場合は、導入療法の変更、あるいは再発・難治例に対する治療を選択。
* 65歳で移植適応の可否を判断するのは目安であり、個々の患者ごとに判断する。
$ MPB療法の初期治療における投与コース数の至適化に関するエビデンスは存在しないアルキル化薬を使用しており、二次がんのリスクも考慮してMPB療法の第III相試験で実施された9コースを記載した。
$$ Ld療法は18コースまでの実施が推奨されるが、それ以後の継続投与が生存期間を延長するというエビデンスはない。患者ごとに効果、費用と副作用を考慮して相談の上で決定すること。
! M蛋白増加速度が速い、LDH上昇などaggressive relapseや高リスク染色体病型は直ちに救援療法導入を推奨。M蛋白増加速度が緩やかなbiochemical relapseは4～6週ごとに経過観察しつつ治療開始時期を判断する。
同種造血幹細胞移植は移植片対骨髄腫効果が期待できるが、治療関連死亡のリスク高く、研究的治療との位置づけである。

1.6.3 海外ガイドライン（NCCN）

- National Comprehensive Cancer Network (NCCN) guidelines Multiple Myeloma, Version 3.2021

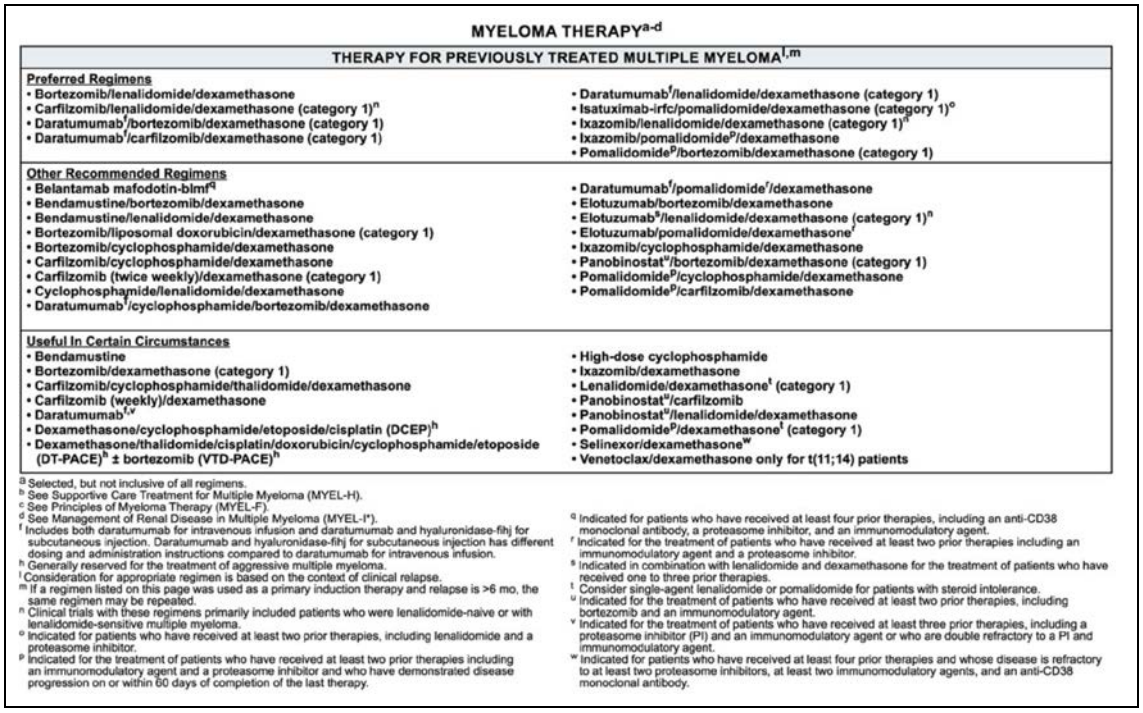
NCCN GUIDELINES®　Multiple Myeloma, Version 3.2021

MYELOMA THERAPY[a-d]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens • **Bortezomib/lenalidomide/dexamethasone (category 1)[j]** • **Daratumumab[f]/lenalidomide/dexamethasone (category 1)** • **Lenalidomide/low-dose dexamethasone (category 1)[k]** • **Bortezomib/cyclophosphamide/dexamethasone[e]**
Other Recommended Regimens • **Carfilzomib/lenalidomide/dexamethasone** • **Ixazomib/lenalidomide/dexamethasone** • **Daratumumab[f]/bortezomib/melphalan/prednisone (category 1)** • **Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone**
Useful In Certain Circumstances • **Bortezomib/dexamethasone** • **Cyclophosphamide/lenalidomide/dexamethasone** • **Carfilzomib/cyclophosphamide/dexamethasone[g]**

MAINTENANCE THERAPY
Preferred Regimens • **Lenalidomide (category 1)**
Other Recommended Regimens • **Bortezomib**
Useful In Certain Circumstances • **Bortezomib/lenalidomide**

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of MyelomaTherapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[g] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[j] This is the only regimen shown to have overall survival benefit.
[k] Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.



MYELOMA THERAPY[a-d]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[l,m]

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)[n]
- Daratumumab[f]/bortezomib/dexamethasone (category 1)
- Daratumumab[f]/carfilzomib/dexamethasone (category 1)
- Daratumumab[f]/lenalidomide/dexamethasone (category 1)
- Isatuximab-irfc/pomalidomide/dexamethasone (category 1)[o]
- Ixazomib/lenalidomide/dexamethasone (category 1)[n]
- Ixazomib/pomalidomide[p]/dexamethasone
- Pomalidomide[p]/bortezomib/dexamethasone (category 1)

Other Recommended Regimens

- Belantamab mafodotin-blmf[q]
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab[f]/pomalidomide[r]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Elotuzumab[s]/lenalidomide/dexamethasone (category 1)[n]
- Elotuzumab/pomalidomide/dexamethasone[t]
- Ixazomib/cyclophosphamide/dexamethasone
- Panobinostat[u]/bortezomib/dexamethasone (category 1)
- Pomalidomide[p]/cyclophosphamide/dexamethasone
- Pomalidomide[p]/carfilzomib/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Bortezomib/dexamethasone (category 1)
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Daratumumab[f,v]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[h]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[h] ± bortezomib (VTD-PACE)[h]
- High-dose cyclophosphamide
- Ixazomib/dexamethasone
- Lenalidomide/dexamethasone[t] (category 1)
- Panobinostat[u]/carfilzomib
- Panobinostat[u]/lenalidomide/dexamethasone
- Pomalidomide[p]/dexamethasone[t] (category 1)
- Selinexor/dexamethasone[w]
- Venetoclax/dexamethasone only for t(11;14) patients

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[h] Generally reserved for the treatment of aggressive multiple myeloma.
[l] Consideration for appropriate regimen is based on the context of clinical relapse.
[m] If a regimen listed on this page was used as a primary induction therapy and relapse is >6 mo, the same regimen may be repeated.
[n] Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[o] Indicated for patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.
[p] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[q] Indicated for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.
[r] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor.
[s] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[t] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.
[u] Indicated for the treatment of patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent.
[v] Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[w] Indicated for patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

本剤は新たな薬理作用を有するボルヒアルロニダーゼ アルファを配合することにより，Dara IV（Dara IV：500～1000mL）と比較して投与時の液量を減らす（本剤：15mL）ことが可能となった。これにより，本剤は短時間の皮下投与が可能となり，Dara IV と比較して投与時の容量負荷リスク軽減が期待されるとともに，IRR 発現率が低減されることが示されている。

本剤の臨床試験では、国内外で実施された 4 試験において有効性・安全性、治療満足度スコア、投与時間及び IRR の発現率が評価された。第Ⅲ相試験の結果から本剤と Dara IV は有効性において非劣性が検証された。また、安全性（特に IRR 発現率）の改善、治療満足度スコアの改善において有用性が認められた。

- IRR 発現率の臨床試験結果

MMY3012 試験ではダラツムマブ投与に伴う IRR の発現率が主要な副次評価項目で評価されており，IRR 発現率は Dara IV 群（34.5%）と比較して本剤群（12.7%）で有意に低かった［オッズ比＝0.28 (95% CI: 0.18,0.44)，p<0.0001］。

- 治療満足度スコアの臨床試験結果

MMY3012 試験では，がん治療満足度質問票改変版（改変 CTSQ）を用いて被験者の治療満足度を患者報告アウトカムで評価した。改変 CTSQ を用いた評価では，がん治療（静脈内投与／皮下投与）に関する被験者満足度及び考えを調査した。がん治療の満足度に関する質問 7 項目の総合的な平均スコアは，評価期間を通して Dara IV 群と比較して本剤群で良好であった。

加えて、Dara IV による治療は大量の輸液を用いて長時間の投与が必要であることから，初回約 7 時間，2 回目以降約 3～4 時間と長時間の投与時間が必要であり，長時間の拘束による患者に与える身体的負担は大きい。また，投与時間の長さから入院を要することも課題とされてきた。ダラツムマブによるMM 治療は疾患増悪まで継続し，患者によっては長期間にわたる投与が必要

であることから，実臨床上ではより簡便な治療が望まれていた。

本剤の投与時間は約 3～5 分となり，Dara IV と比べて大幅な投与時間の短縮が可能となる。臨床試験では本剤と Dara IV の投与時間が評価され，本剤は Dara IV と比較して投与時間が大幅に短縮できることが示された。また，Dara IV では輸液ポンプを用いて点滴速度を管理し，さらに投与中に初回投与及び 2 回目の投与では少なくとも 3 回，その後の投与では少なくとも 2 回点滴速度を変更する必要があり，その対応とモニタリングは医療従事者にとって負担となる。また投与速度調整ミスによる，不適切な点滴速度での投与リスクも生じる。一方，本剤ではそれらの必要がなく，医療従事者の負担軽減と投与速度調整ミスによる不適切な点滴速度での投与リスクが軽減できる。このように，本剤は Dara IV と比較して投与の利便性を高めることで，医療従事者の薬剤調製負担の軽減・医療過誤の低減，医療従事者の患者ケアにかかる負担の軽減が期待できる。

本剤が医療従事者にもたらす負担軽減は，投与に関連する医療行為の時間短縮を確認した調査結果[5]からも示されている。本剤の国際共同第Ⅲ相試験（MMY3012 試験）に患者の組み入れを実施した施設のうち本剤の投与経験があり、かつ本調査への参加に合意が得られた施設を対象に、医療行為に要する時間の調査結果を実施した。その結果、医療従事者による医療行為に要する時間に要する時間は初回投与では 63.8%，2 回目以降では 49.5%、それぞれ短縮された。患者の拘束時間は Dara IV と比較して 97%減少した。

以上より，本剤はダラツムマブの皮下投与による簡便な治療を可能とし，投与における利便性を著しく向上させ，患者と医療従事者の双方に高い医療上の有用性をもたらすと考えられる。また，ダラツムマブ投与のための入院によるベッドを開放できる事は，大きな医療上の有用性と考えられる。

1.7 主な有害事象

本剤の重大な副作用として以下の副作用が該当する。

・Infusion related reaction (IRR)
・骨髄抑制
・感染症
・腫瘍崩壊症候群(TLS)
・間質性肺疾患

各事象につき、推奨されている対応方法は以下の通りである。

- Infusion related reaction
  - Infusion related reaction の管理を適切に実施できる体制下で本剤を投与する。
  - 発現した場合は、必要に応じて、本剤の中止等を含めた適切な治療を行う。
  - Infusion related reaction を軽減させるため、副腎皮質ホルモン剤、解熱鎮痛剤、抗ヒスタミン剤による前投与を実施する。

- 遅発性の infusion related reaction(本剤投与開始から 24 時間以降に発現)を軽減させるため、必要に応じて副腎皮質ホルモン剤等による投与後処置を実施する。
- 本剤投与中及び投与後は infusion related reaction の症状がないか十分に観察する。

- 骨髄抑制
  - 関連検査値のモニタリングを実施し、好中球減少が発現した場合は、必要に応じて、本剤の中止、併用薬剤の休薬及び減量、G-CSF 治療等を考慮する。
  - 関連検査値のモニタリングを実施し、血小板減少が発現した場合は、必要に応じて、本剤の中止、併用薬剤の休薬及び減量、血小板輸血等を考慮する。
- 感染症
  - 異常が認められた場合は、必要に応じて、本剤の中止等を含めた適切な治療を行う。
- 腫瘍崩壊症候群(TLS)
  - 高腫瘍量等のハイリスク患者では適切な予防措置及び注意深いモニタリングを実施する。
- 間質性肺疾患
  - 間質性肺疾患の初期症状(息切れ、呼吸困難、咳嗽、発熱等)が発現した場合には、必要に応じて、胸部 X 線検査、胸部 CT 検査、血清マーカー等の検査を実施し、適切な処置を行う。

1.8 他国の医療技術評価機関における評価結果

医療技術評価機関における評価結果を以下に要約した。

- 表 1-3 医療技術評価機関における評価結果

国名	機関名	評価結果 (記載例)	リスト価格 (現地通貨建)
イギリス	NICE (TA)	**その他** ([redacted])	[redacted] GBP
	SMC	**推奨** (Based on Abbreviated submission. Reimbursed in previously recommended regimen for Dara IV)	
フランス	HAS	・SMR: Important ・ASMR: V (vs DARA IV) ・**効率性評価:不要**	[redacted] EUR
ドイツ	IQWiG (早期有	**その他** ([redacted])	[redacted] EUR

国名	機関名	評価結果 (記載例)	リスト価格 (現地通貨建)
	用性評価)		
カナダ	CADTH (CDR/pCODR)	**その他** ([redacted] [redacted]	[redacted] CAD
オーストラリア	PBAC	**推奨**(Based on a cost minimization basis with Dara IV)	[redacted] AUD

また各国における医療経済評価の詳細は以下の通りであった。

- 表 1-4 医療技術評価機関における評価結果の有無

国名	機関名	評価結果の有無
イギリス	NICE	なし
	SMC	あり(Based on Abbreviated submission. Reimbursed in previously recommended regimen for Dara IV)(効率性評価:不要)
フランス	HAS	あり(効率性評価:不要)
ドイツ	IQWiG	なし
カナダ	CADTH	なし
オーストラリア	PBAC	あり(費用最小化分析)

また評価結果の詳細は以下の通りであった。

- 表 1-5 医療技術評価機関における評価結果

国名	オーストラリア
機関名	PBAC
評価結果の URL など	https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-07/files/daratumumab-psd-july-2021.pdf
評価対象技術	Dara SC
評価結果	推奨
条件付き推奨の場合は、その条件の詳細	PBAC は、Dara SC が Dara IV に対して確立されている既存の構成に追加されることが妥当であると判断した。
評価対象疾患	RRMM

	多発性骨髄腫; 1 種類以上の前治療ののちに再発又は難治性となった患者（すなわち、2nd line の MM 患者）。
使用方法 (※)	Dara IV が使用されているすべての適応症のレジメンに対して; ・ 1 種類以上の前治療歴を有する MM 患者の治療を目的とした Rd 併用療法又は Vd 併用療法 ・ プロテアソーム阻害薬（PI）及び免疫調節薬を含む 3 レジメン以上の前治療歴を有する、又は PI 及び免疫調節薬の両方に難治性の MM 患者への単剤療法 ・ VMP との併用で、新規に MM と診断され、自家幹細胞移植（ASCT）に不適格な患者の治療
比較対照	Dara IV
主要な増分費用効果比の値	Dara IV を比較対照とした費用最小化分析の結果に基づき薬価が算定された。申請者は年間コストをベースとした費用最小化分析を実施し、PBAC はそれを合理的であるとみなした。分析の中で Dara SC の平均投与期間は [redacted]、Dara IV の平均投与期間は [redacted]、と設定された。PBAC はスケジュール間のマークアップの違いにより若干の違いはあるものの、Dara SC は Dara IV と比較して本質的にコスト中立であるとした。この勧告を行うにあたり、PBAC は Dara SC が生活の質の改善及び利便性において Dara IV と比較して優れているという消費者の意見に同意した。

2．費用効果分析における分析条件の設定

2.1 分析対象とする集団

[主要分析]

造血幹細胞移植の適応とならない未治療の多発性骨髄腫及び再発又は難治性の多発性骨髄腫

[その他：HCP の時間的観点からの費用差]：主要分析と同じ

[その他：シナリオ分析]

再発・難治の 2 次治療以降の患者*

*ダラキューロ（MM）の費用対効果評価に関わる分析枠組み決定の際に、費用対効果評価専門組織において感度分析の位置づけとして本集団に対するシナリオ分析の実施が決定した。

2.2 比較対照

[主要分析]

Dara IV

- 選定理由

Dara SC と Dara IV の添付文書上の効能または効果、投与間隔は同一であることから、Dara IV が比較対象技術として適切である。また NCCN ガイドラインにおいても、Dara SC はすべてのダラツムマブ投与レジメンにおいて Dara SC と区別されていない。

1) Dara IV は、本剤が分析対象集団の治療に導入される時点以降で、大部分患者が本剤により置き換えられると予想される。

2) Dara IV は、本剤の国際共同第Ⅲ相ランダム化比較試験における対照薬であり、薬理作用は同一である。また薬価算定における最類似薬である。

3) ダラツムマブは MM 治療における有用な薬剤であり、TIE NDMM 患者及び RRMM 患者に対して、国内外の診療ガイドラインで推奨されている。TIE NDMM 患者に対して、ダラツムマブは、日本血液学会及び日本骨髄腫学会の診療ガイドラインにおいて推奨治療レジメンすべてに含まれている唯一の薬剤である。RRMM 患者に対してダラツムマブは、日本血液学会の診療ガイドラインにおいて、より良好な転機をもたらすとして、カテゴリー1 のエビデンスで裏付けられた推奨レジメンである。また、NCCN ガイドラインでは、ダラツムマブは、NCCN ガイドラインのカテゴリー1 のエビデンスで裏付けられた推奨レジメンとして臨床現場で使用されている。本剤は、すべてのダラツムマブ治療レジメンにおいて Dara IV と併記されている。国内ガイドラインにおいても、有効性を維持しつつ利便性と安全性を大きく改善する本剤は Dara IV と同様に推奨されることが想定される。

[その他：HCP の時間的観点からの費用差]：主要分析と同じ

[その他：シナリオ分析]

費用対効果評価専門組織において「最も費用対効果のよい治療法」を選択し RRMM 患者における分析の比較対照とすることが決定された。本決定について弊社と C2H による議論の上、Vd お

よび Rd を比較対照とすることが合意された。

- 選定理由

弊社が実施した MDV データベースを使用した MM の治療パターン分析（一部の結果を第46回日本骨髄腫学会学術集会において発表した[6]）において、RRMM における 2 次治療の各治療法の頻度と割合を集計し、Vd および Rd の 2 つの治療法は広く一般的に使用されていると考えられた。またこの 2 つの治療法は他の HTA 評価国で広く償還されており、その費用対効果は十分に確立されていると考えられる。

2.3 分析の立場と費用の範囲

ガイドラインの原則に基づき、分析の立場は公的医療の立場、費用の範囲は公的医療費とした。
その他の分析における除外：HCP の時間的観点からの費用差の分析は、HCP の時間的観点から費用差を検討するために実施した。

2.4 効果指標

[主要分析]
費用最小化分析：有効性が同等であると仮定して、費用による比較を行った。
[その他：HCP の時間的観点からの費用差] なし（費用のみ）
[その他：シナリオ分析]
費用効用分析：ガイドラインの原則に基づき、効果指標は QALY とした。

2.5 分析期間

[主要分析]
費用最小化分析：弊社が実施し第46回日本骨髄腫学会学術集会において発表した MDV データベース(2019 年 8 月データ)を使用した MM の治療パターン分析と同様の解析を MDV データベース(2021 年 5 月データ)に対して行い、Dara IV の平均投与期間を集計したところ、TIE NDMM と RRMM においてそれぞれ 32 週間であった。Dara SC の実際の投与期間はデータから得られなかったため、Dara SC と Dara IV の投与期間は同じであると仮定した。以上より、分析期間は 32 週間、また感度分析として分析期間を 52 週間(1 年)とした分析を実施した。
[その他：HCP の時間的観点からの費用差]
患者あたりの薬剤投与のための来院
[その他：シナリオ分析]
費用効用分析：生涯 (30 年)

2.6 割引率

[主要分析]

費用最小化分析:32 週間および 1 年間の分析であるため割引を行わなかった。

[その他:HCP の時間的観点からの費用差]

なし(分析期間≤ 1 年)

[その他:シナリオ分析]

費用効用分析:ガイドラインの原則に基づき、割引率は、費用、効果共に年率 2%とした。

2.7 分析条件の設定の要約

	主要分析	その他:HCP の時間的観点からの費用差
分析対象とする集団	造血幹細胞移植の適応とならない未治療の多発性骨髄腫及び再発又は難治性の多発性骨髄腫(TIE NDMM & RRMM)	造血幹細胞移植の適応とならない未治療の多発性骨髄腫及び再発又は難治性の多発性骨髄腫(TIE NDMM & RRMM)
比較対照	Dara IV	Dara IV
比較対照を選定した理由	Dara SC と Dara IV の添付文書上の効能または効果、投与間隔は同一であることから、Dara IV が比較対照技術として適切である。また NCCN ガイドラインにおいても、Dara SC はすべてのダラツムマブ投与レジメンにおいて Dara SC と区別されていない。	Dara SC と Dara IV の添付文書上の効能または効果、投与間隔は同一であることから、Dara IV が比較対照技術として適切である。また NCCN ガイドラインにおいても、Dara SC はすべてのダラツムマブ投与レジメンにおいて Dara SC と区別されていない。
分析の立場と費用の範囲	公的医療の立場 公的医療費のみ	HCP の時間的観点
効果指標	公的医療費	なし(時間および費用のみ)
分析期間	主要分析:32 週間 感度分析:52 週間	患者あたりの薬剤投与のための来院
割引率	なし	なし

	その他:シナリオ分析
分析対象とする集団	再発又は難治性の多発性骨髄腫(RRMM)
比較対照	Vd 及び Rd

	その他:シナリオ分析
比較対照を選定した理由	費用対効果評価専門組織において「最も費用対効果のよい治療法」を選択し RRMM 患者における分析の比較対照とすることが決定された。本決定について弊社と C2H による議論の上、Vd および Rd を比較対照とすることが合意された。 この 2 つの治療法は広く一般的に使用されていると考えられた。またこの 2 つの治療法は他の HTA 評価国で広く償還されており、その費用対効果は十分に確立されていると考えられる。
分析の立場と費用の範囲	公的医療の立場 公的医療費のみ
効果指標	QALY、生存年
分析期間	生涯（30 年）
割引率	費用･効果ともに年率 2%

3. Additional Benefits

3.1 Clinical Questions

A systematic literature review (SLR) of randomized clinical trials (RCTs) to examine additional benefit of daratumumab subcutaneous injection (Dara SC) among multiple myeloma patients with transplant ineligible newly diagnosed multiple myeloma (TIE NDMM) and relapsed or refractory multiple myeloma (RRMM) was conducted based on the research questions.

As agreed by expert committee meeting (on 27th August, 2021), the main analysis will focus on the target population of patients with multiple myeloma (including TIE NDMM and RRMM). The intervention is Dara SC and the comparator is daratumumab intravenous infusion (Dara IV).

Separately, other analysis was requested to focusing on RRMM patients and the comparator are set to be bortezomib in combination with dexamethasone (Vd) and lenalidomide in combination with dexamethasone (Rd). After initial search, a study was identified to directly comparing DARA SC and DARA IV, however, there were no study identified directly comparing Dara SC with other selected comparators. The search was therefore broadened to include Dara IV assuming similar efficacy between Dara IV and SC based on the main analysis.

For each of the two research questions, a search strategy was developed using the designated databases. The outcomes were efficacy, safety and patient reported outcome (PRO). The time frame of the systematic literature search was from 1st January 2011 to 31st October 2021 for the main analysis and scenario analysis as presented in Table 3-1 and Table 3-2.

- Table 3-1 Research questions of systematic review – main analysis

Item	Description
Population	Multiple myeloma (including transplant ineligible NDMM and RRMM)
Intervention	Daratumumab SC
Comparator	Daratumumab IV
Outcome	• Efficacy (ORR, PFS, OS) • Safety • HRQoL
Study design	Randomized controlled trial
Literature search period	1st January 2011 to 31st October 2021

HRQoL: health-related quality of life; IV: intravenous; NDMM: newly diagnosed multiple

myeloma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; Rd: Revlimid (Lenalidomide) + Dexamethasone; RRMM: relapsed refractory multiple myeloma; SC: subcutaneous; Vd: Velcade (Bortezomib) + Dexamethasone

- Table 3-2 Research questions of systematic review – scenario analysis

Item	Description
Population	RRMM (1L+)
Intervention	Daratumumab (SC and IV*)
Comparator	Vd and Rd
Outcome	• Efficacy (ORR, PFS, OS) • Safety • HRQoL
Study design	Randomized controlled trial
Literature search period	1st January 2011 to 31st October 2021

1L: first line of treatment; HRQoL: health-related quality of life; IV: intravenous; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; Rd: Revlimid (Lenalidomide) + Dexamethasone; RRMM: relapsed refractory multiple myeloma; SC: subcutaneous; Vd: Velcade (Bortezomib) + Dexamethasone

* As there were no study identified comparing Dara SC with the comparator. The search was therefore broadened to include Dara IV assuming similar efficacy between Dara IV and SC.

3.2 Systematic Review

3.2.1 Implementation flow

In the literature search process, an expert of literature search developed the search formula by combining conditions for disease name, drug name, study design, and search period. Screening based on publication abstracts and the following operation to identify relevant RCTs for the evaluation of additional benefit were performed with blinding by two independent reviewers. Inclusion or exclusion of publications was determined based on the prespecified criteria. Those eligible for inclusion were selected for full text screening and independent review. Discrepancies were resolved by involving a third investigator and reaching consensus. Articles meeting criteria at the full-text stage were included in the analysis. Publications and conference abstracts were selected for extracting the relevant data including the post hoc, updated and subgroup analyses. The RCTs identified were summarized in a table form with a summary of results.

3.2.2 Inclusion and exclusion criteria

The key inclusion and exclusion criteria for the SLR are presented as follows.

3.2.2.1 Inclusion criteria

- The target disease is patients with transplant ineligible NDMM or RRMM for the main analysis and RRMM patients for the scenario analysis.
- The intervention is Dara SC (for scenario analysis, at the initial search, we set the intervention as Dara SC; since, no study was found initially, the search was broadened to include Dara IV assuming similar efficacy between Dara IV and SC).
- The comparator is Dara IV for the main analysis and Rd and Vd for the scenario analyses.
- The study design is randomized controlled trial.
- Published during the designated period (1st January 2011 to 31st October 2021).

3.2.2.2 Exclusion criteria

- Meeting minutes or conference details
- Not written in English or Japanese

3.2.3 Database

PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Ichushi-Web, J-stage and ClinicalTrials.gov were used for collection of the target studies.

3.2.3.1 Search formula

Main analysis

The search formulas for the SLR for main analysis are presented as follows, which compared Dara SC and Dara IV.

Search formula for PubMed
Date of search: November 02, 2021
#1. (((multiple myelomas[MeSH Terms]) OR ("multiple myeloma")) OR (myeloma-multiple)) OR ("myeloma multiple") #2. (#1) NOT ("transplant-eligible" OR "AL amyloidosis" OR "before and after autologous stem-cell transplantation " OR "triple-class refractory multiple

myeloma" OR "smoldering multiple myeloma") #3. ((Daratumumab[Title/Abstract]) AND (subcutaneous[Title/Abstract])) OR (DARA-SC OR "DARA SC" OR DARZQURO) #4. ((Daratumumab[Title/Abstract]) AND (intravenous[Title/Abstract])) OR (DARA-IV[Title/Abstract] OR "DARA IV"[Title/Abstract] OR DARZALEX[Title/Abstract]) #5. ((Randomized Controlled Trial[Publication Type]) OR ((randomized[Title] OR randomised)[Title] AND (trial[Title] OR trials)[Title])) OR (randomized controlled trials as topic[MeSH Terms]) #6. #2 AND #3 AND #4 AND #5 #7. #2 AND #3 AND #4 AND #5: Filter 2011 to 2021
Number of publications: 05

Search formula for Embase and Cochrane
Date of search: November 02, 2021
#1. ("multiple myelomas" or "multiple myeloma" or myeloma-multiple or "myeloma multiple").mp. #2. ("transplant-eligible" or "AL amyloidosis" or "before and after autologous stem-cell transplantation " or "triple-class refractory multiple myeloma" or "smoldering multiple myeloma").mp. #3. 1 not 2 #4. ((Daratumumab and subcutaneous) or (DARA-SC or "DARA SC" or DARZQURO)).ti,ab. #5. ((Daratumumab and intravenous) or (DARA-IV or "DARA IV" or DARZALEX)).ti,ab. #6. ("Randomized Controlled Trial" or ((randomized or randomized) and (trial or trials)) or randomized controlled trials).ti,ab.

#7. 3 and 4 and 5 and 6 #8. remove duplicates from 7
Number of publications: 14

Search formula for Ichushi Web, J-stage and Clinical trials.gov
Date of search: November 02, 2021
Used keyword: “Daratumumab”
Number of publications • Ichushi Web: 302 • J-stage: 122 • Clinical Trials.gov: 184

Scenario analysis – initial search

The search formulas for the SR for scenario analysis comparing Dara SC with Rd and Vd are presented as follows.

Search formula for PubMed
Date of search: November 02, 2021
#1. (((multiple myelomas[MeSH Terms]) OR ("multiple myeloma")) OR (myeloma-multiple)) OR ("myeloma multiple") #2. (#1) NOT ("transplant-eligible" OR "AL amyloidosis" OR "before and after autologous stem-cell transplantation " OR "triple-class refractory multiple myeloma" OR "smoldering multiple myeloma") #3. ((Daratumumab[Title/Abstract]) AND (subcutaneous[Title/Abstract])) OR (DARA-SC OR "DARA SC" OR DARZQURO) #4. ((Bortezomib OR Velcade) AND Dexamethasone) OR ((Lenalidomide OR Revlimid) AND Dexamethasone) #5. ((Randomized Controlled Trial[Publication Type]) OR ((randomized[Title] OR randomised)[Title] AND (trial[Title] OR trials)[Title])) OR (randomized controlled trials as topic[MeSH Terms])

#6. #2 AND #3 AND #4 AND #5
Number of publications: 0

Search formula for Embase and Cochrane
Date of search: November 02, 2021
#1. ("multiple myelomas" or "multiple myeloma" or myeloma-multiple or "myeloma multiple").mp. #2. ("transplant-eligible" or "AL amyloidosis" or "before and after autologous stem-cell transplantation " or "triple-class refractory multiple myeloma" or "smoldering multiple myeloma").mp. #3. 1 not 2 #4. ((Daratumumab and subcutaneous) or (DARA-SC or "DARA SC" or DARZQURO)).ti,ab. #5. ((Bortezomib or Velcade) and Dexamethasone).mp. or ((Lenalidomide or Revlimid) and Dexamethasone).ti,ab. #6. ("Randomized Controlled Trial" or ((randomized or randomized) and (trial or trials)) or randomized controlled trials).ti,ab. #7. 3 and 4 and 5 and 6 #8. remove duplicates from 7
Number of publications: 9 (*NONE* of the records are relevant to inclusion criteria after checking)

Search formula for Ichushi Web, J-stage and Clinical trials.gov
Date of search: November 02, 2021
Used keyword: “Daratumumab”
Number of publications: • Ichushi Web: 302 • J-stage: 122

• Clinical Trials.gov: 184 (*NONE* of the records are relevant to inclusion criteria after checking)

Since no studies met the inclusion criteria comparing Dara SC with the comparators (Rd and Vd), the search was extended to include Dara IV.

Scenario analysis – the extended search

The search formulas for the SR for scenario analysis comparing Dara IV with Rd and Vd are presented below.

Search formula for PubMed
Date of search: November 02, 2021
#1. (((multiple myelomas[MeSH Terms]) OR ("multiple myeloma")) OR (myeloma-multiple)) OR ("myeloma multiple") #2. (#1) NOT ("transplant-eligible" OR "AL amyloidosis" OR "before and after autologous stem-cell transplantation " OR "triple-class refractory multiple myeloma" OR "smoldering multiple myeloma") #3. Daratumumab[Title/Abstract] #4. ((Bortezomib OR Velcade) AND Dexamethasone) OR ((Lenalidomide OR Revlimid) AND Dexamethasone) #5. ((Randomized Controlled Trial[Publication Type]) OR ((randomized[Title] OR randomised)[Title] AND (trial[Title] OR trials)[Title])) OR (randomized controlled trials as topic[MeSH Terms]) #6. #2 AND #3 AND #4 AND #5 #7. #2 AND #3 AND #4 AND #5: Filter 2011 to 2021
Number of publications: 47

Search formula for Embase and Cochrane
Date of search: November 02, 2021
#1. ("multiple myelomas" or "multiple myeloma" or myeloma-multiple or

"myeloma multiple").mp. #2. ("transplant-eligible" or "AL amyloidosis" or "before and after autologous stem-cell transplantation " or "triple-class refractory multiple myeloma" or "smoldering multiple myeloma").mp. #3. 1 not 2 #4. Daratumumab.ti,ab. #5. ((Bortezomib or Velcade) and Dexamethasone).mp. or ((Lenalidomide or Revlimid) and Dexamethasone).ti,ab. #6. ("Randomized Controlled Trial" or ((randomized or randomized) and (trial or trials)) or randomized controlled trials).ti,ab. #7. 3 and 4 and 5 and 6 #8. Remove duplicates from 7
Number of publications: 131

Search formula for Ichushi Web, J-stage and Clinical trials.gov
Date of search: November 02, 2021
Used keyword: “Daratumumab”
Number of publications: two records were found to be relevant as per inclusion criteria • Ichushi Web: 302 • J-stage: 122 • Clinical Trials.gov: 184

3.2.4 Conference search

The search also included the following conference proceedings:

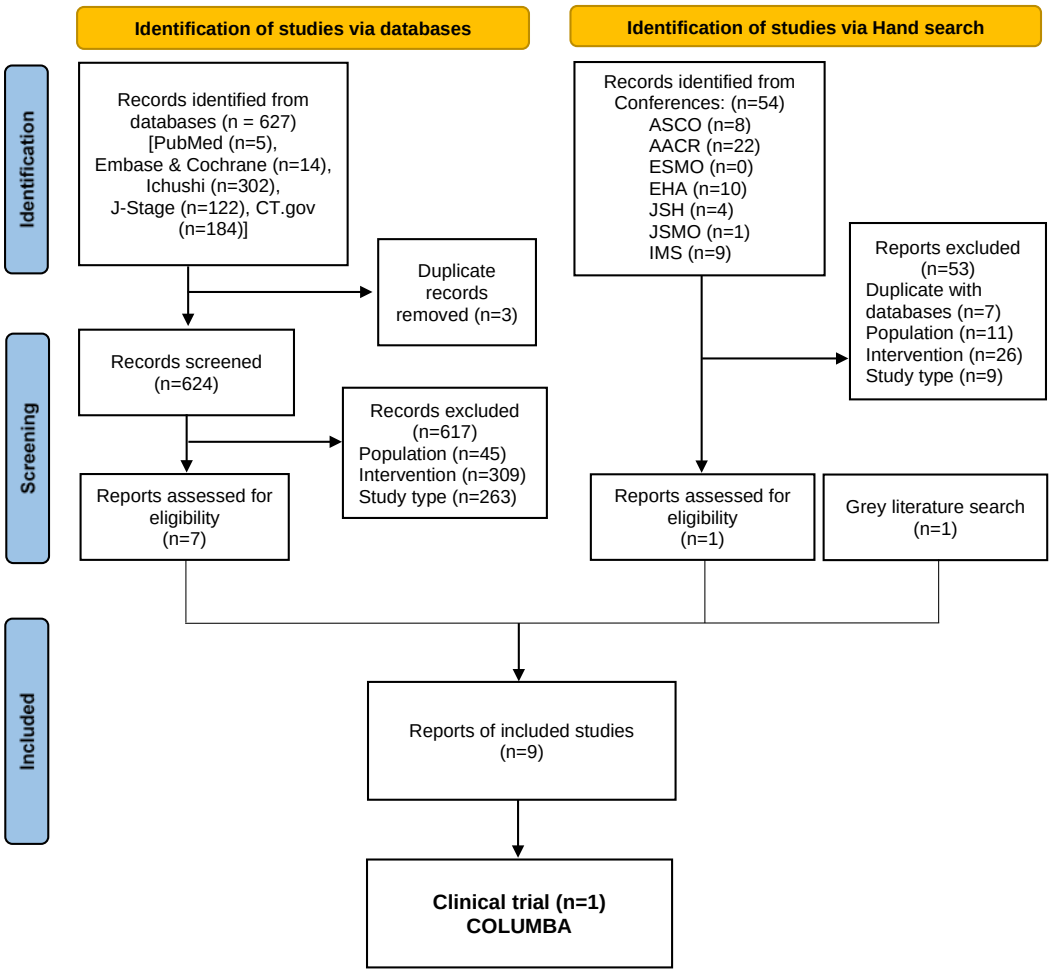
- American Society for Clinical Oncology (ASCO);
- American Association for Cancer Research (AACR);
- European Society of Medical Oncology (ESMO);

- European Hematology Association (EHA);
- Japanese Society of Hematology (JSH) and
- Japanese Society of Medical Oncology (JSMO).

3.2.5 Search results

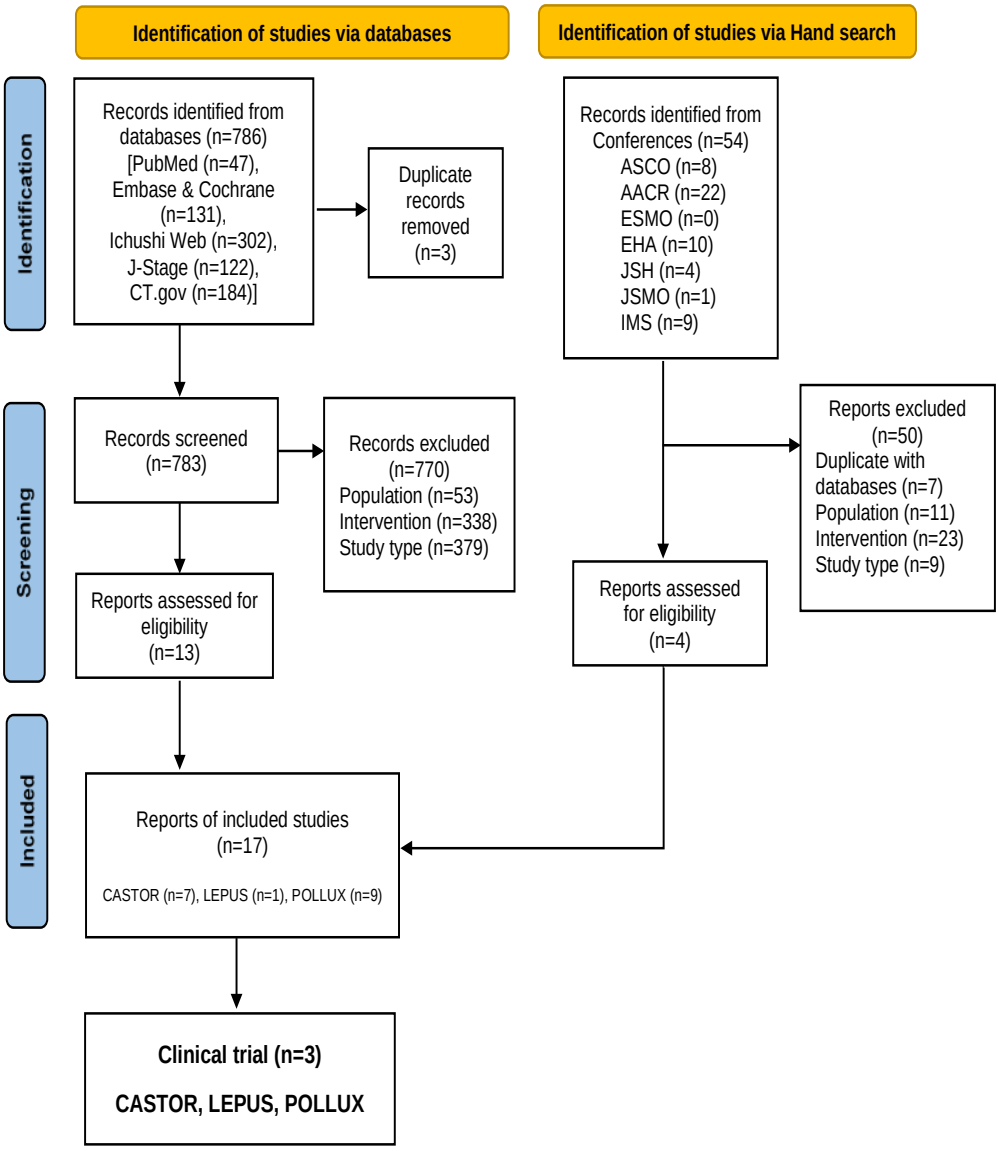
The results of the SLR were summarized as shown in Figure 3-1 and Figure 3-2 with reference to the flow chart recommended by PRISMA Statement.

- Figure 3-1 PRISMA statement for the main analysis



AACR: American Association for Cancer Research; ASCO: American Society of Clinical Oncology; EHA: European Hematology Association; ESMO: European Society for Medical Oncology; IMS: International Myeloma Society; JSH: Japanese Society of Hematology; JSMO: Japanese Society of Medical Oncology

- Figure 3-2 PRISMA statement for the scenario analysis



AACR: American Association for Cancer Research; ASCO: American Society of Clinical Oncology; EHA: European Hematology Association; ESMO: European Society for Medical Oncology; IMS: International Myeloma Society; JSH: Japanese Society of Hematology; JSMO: Japanese Society of Medical Oncology

3.2.6 Listing of clinical studies identified

- Table 3-3 List of identified clinical studies – Main analysis: COLUMBA; scenario analysis: CASTOR, LEPUS and POLLUX

Clinical study	Intervention	Comparator	Sample size	Statistics	Primary analysis publication
Main analysis					
COLUMBA	Dara SC	Dara IV	• Dara SC: n=263 • Dara IV: n=259	• The Kaplan-Meier method was used to estimate time-to-event distributions. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model.	Mateos et. al. 2020[7]
Scenario analysis*					
CASTOR	Dara IV + Vd	Vd	• Dara IV + Vd: n=251 • Vd: n=247	• The log-rank test method was used to compared both groups. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The Kaplan–Meier method was used to estimate the distributions. • A stratified Cochran–Mantel–Haenszel chi-square test was used to test between-group differences in the	Palumbo et. al. 2016[8]

Clinical study	Intervention	Comparator	Sample size	Statistics	Primary analysis publication
				overall response rate.	
LEPUS	Dara IV+ Vd	Vd	• Dara IV + Vd: n=141 • Vd: n=70	• The Kaplan–Meier method was used to estimate the distributions. • A stratified Cox regression model with treatment as the sole explanatory variable was used to estimate HRs and 95% confidence intervals. • A stratified Cochran–Mantel–Haenszel chi-square test was used to measure treatment differences in the overall response rate, ≥very good partial response rate, and ≥CR rate.	Lu et. al. 2021[9]
POLLUX	Dara IV + Rd	Rd	• Dara IV + Rd: n=286 • Rd: n=283	• Stratified log-rank test method was used to compared both groups. • Hazard ratios and 95% confidence intervals were estimated with the use of a Cox regression model, with treatment as the sole explanatory variable.	Dimopoulos et. al. 2016[10]

Clinical study	Intervention	Comparator	Sample size	Statistics	Primary analysis publication
				• Cochran–Mantel–Haenszel tests were used to compare overall response rates, rates of very good partial response or better, and other binary end points.	

Dara: daratumumab; IV: intravenous; Rd: Revlimid + dexamethasone; SC: subcutaneous; Vd: Velcade + dexamethasone

* As there were no study identified comparing Dara SC with the comparator. The search was broadened to include Dara IV assuming similar efficacy between Dara IV and SC.

3.2.7 Summary of additional benefit assessment

3.2.7.1 Main analysis

COLUMBA clinical trial

The methodology of the systematic review performed to examine additional benefit of daratumumab was generally appropriate. Through the systematic review, following publications related to the RCTs to evaluate the efficacy and safety of daratumumab were identified. Publications (1), (2) and (3) were original articles identified from databases and were associated with COLUMBA trial. Publication (4) was identified through grey literature search. Publications (5) to (9) were records of presentation at scientific meetings.

(1) Mateos MV, Nahi H, Legiec W, et. al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol. 2020 May;7(5):e370-e380. doi: 10.1016/S2352-3026(20)30070-3.[7]

(2) Usmani SZ, Mateos MV, Hungria V, et. al. Greater treatment satisfaction in patients receiving daratumumab subcutaneous vs. intravenous for relapsed or refractory multiple myeloma: COLUMBA clinical trial results. J Cancer Res Clin Oncol. 2021 Feb;147(2):619-631. doi: 10.1007/s00432-020-03365-w.[11]

(3) Iida S, Ishikawa T, Min CK, et. al. Subcutaneous daratumumab in Asian patients with heavily pretreated multiple myeloma: subgroup analyses of the noninferiority, phase 3 COLUMBA study. Ann Hematol. 2021 Apr;100(4):1065-1077. doi: 10.1007/s00277-021-04405-2.[12]

(4) Slavcev M, Spinelli A, Absalon E, Masterson T, Heuck C, Lam A, De Cock E. Results of a Time and Motion Survey Regarding Subcutaneous versus Intravenous Administration of Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma. Clinicoecon Outcomes Res. 2021 Jun 8;13:465-473. doi: 10.2147/CEOR.S302682.[5]

(5) Mateos MV, Usmani SZ, Grosicki S, et. al. Randomized, Open-Label, Non-Inferiority, Phase 3 Study of Subcutaneous (SC) Versus Intravenous (IV) Daratumumab (DARA) Administration in Patients (Pts) with Relapsed or Refractory Multiple Myeloma (RRMM): Body Weight Subgroup Analysis of Columba. Abstract presented at 61st ASH Annual Meeting. Orlando United States. 134(Supplement 1) (pp 1906), 2019.[13]

(6) Usmani SZ, Mateos MV, Nahi H, et. al. Randomized, Open-Label, Non-Inferiority, Phase 3 Study of Subcutaneous (SC) Versus Intravenous (IV) Daratumumab (DARA) Administration in Patients with Relapsed or Refractory Multiple Myeloma: Columba Update. Abstract presented at 61st ASH Annual Meeting. Orlando United States. 134(Supplement 1) (pp 1865), 2019. [14]

(7) Kaiser M, Mateos MV, Usmani SZ, Phase 3, open-label, non-inferiority study of subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma: Body weight subgroup analysis of Columba. Abstract presented at 60th Annual Scientific Meeting of the British Society for Haematology. Birmingham United Kingdom. 189(Supplement 1) (pp 22), 2020.[15]

(8) Mateos MV, Nahi H, Legiec W, et. al. Efficacy and safety of the randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients (pts) with relapsed or refractory multiple myeloma (RRMM): COLUMBA. Annual Meeting of the American Society of Clinical Oncology, ASCO 2019. Chicago, IL United States. 37(Supplement 15) (no pagination), 2019.[16]

(9) Mateos MV, Nahi H, Legiec W, et. al. Randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients with relapsed or refractory multiple myeloma: COLUMBA. Presented at European Hematology Association (EHA), 2019.[17]

The following outcome measures were used for the evaluation of additional benefit:

- Primary outcomes: Overall response
- Secondary outcomes: PFS, OS, PRO, and IRR

3.2.7.2 Scenario analysis

CASTOR clinical trial

Publications (1) was identified as a primary analysis of CASTOR clinical trial and publications (2) to (5) were supporting original articles reporting data for extended follow-up, subgroup analyses and quality of life. Publications (6) and (7) were records of abstract presentation at ASH and EHA conferences, respectively.

(1) Palumbo A, Chanan-Khan A, Weisel K, et. al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Aug 25;375(8):754-66. doi: 10.1056/NEJMoa1606038.[8]

(2) Mateos MV, Sonneveld P, Hungria V, et. al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020 Aug;20(8):509-518. doi: 10.1016/j.clml.2019.09.623.[18]

(3) Spencer A, Lentzsch S, Weisel K, et. al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018 Dec;103(12):2079-2087. doi: 10.3324/haematol.2018.194118.[19]

(4) Weisel K, Spencer A, Lentzsch S, et. al. Daratumumab, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma: subgroup analysis of CASTOR based on cytogenetic risk. J Hematol Oncol. 2020 Aug 20;13(1):115. doi: 10.1186/s13045-020-00948-5.[20]

(5) Hungria V, Beksac M, Weisel KC, et. al. Health-related quality of life maintained over time in patients with relapsed or refractory multiple myeloma treated with daratumumab in combination with bortezomib and dexamethasone: results from the phase III CASTOR trial. Br J Haematol. 2021 May;193(3):561-569. doi: 10.1111/bjh.17321.[21]

(6) Weisel KC, Sonneveld P, Mateos MV et. al. Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) Versus Bortezomib and Dexamethasone (Vd) in First Relapse Patients (pts) with Multiple Myeloma (MM): Four-Year Update of CASTOR. Presented at American Society of Hematology (ASH), 2019.[22]

(7) Weisel K, Spencer A, Lentzsch S, et. al. Efficacy and safety of daratumumab, bortezomib, and dexamethasone (D-Vd) in relapsed or refractory multiple myeloma (RRMM): Updated subgroup analysis of CASTOR based on cytogenetic risk. Presented at European Hematology Association (EHA), 2019.[23]

The manufacturer used the following outcome measures for the evaluation of additional benefit:

- Primary outcomes: PFS
- Secondary outcomes: ORR, OS, safety and HRQoL

LEPUS clinical trial

One publication was identified associated with LEPUS (MMY3009) clinical trial reporting data for daratumumab plus bortezomib and dexamethasone. LEPUS study was conducted to confirm that DVd demonstrates similar efficacy and safety in Chinese patients with RRMM compared with the global phase 3 CASTOR.

(1) Lu J, Fu W, Li W, et. al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in Chinese patients with relapsed or refractory multiple myeloma: Phase 3 LEPUS (MMY3009) study. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):e699-e709. doi: 10.1016/j.clml.2021.04.012.[9]

The manufacturer used the following outcome measures for the evaluation of additional benefit:

- Primary outcomes: PFS
- Secondary outcomes: ORR, OS, and safety

POLLUX clinical trial

Publications (1) was identified as a primary analysis of POLLUX clinical trial and publications (2) to (6) were supporting original articles reporting data for extended follow-up, subgroup analyses and quality of life. Publications (7), (8) and (9) were records of abstract presentation at ASH, 2019 and EHA, 2019 conferences.

(1) Dimopoulos MA, Oriol A, Nahi H, et. al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Oct 6;375(14):1319-1331. doi: 10.1056/NEJMoa1607751.[10]

(2) Bahlis NJ, Dimopoulos MA, White DJ, et. al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020 Jul;34(7):1875-1884. doi: 10.1038/s41375-020-0711-6.[24]

(3) Kaufman JL, Dimopoulos MA, White D, et. al. Daratumumab, lenalidomide, and dexamethasone in relapsed/refractory myeloma: a cytogenetic subgroup analysis of POLLUX. Blood Cancer J. 2020 Nov 3;10(11):111. doi: 10.1038/s41408-020-00375-2.[25]

(4) Dimopoulos MA, San-Miguel J, Belch A, et. al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018 Dec;103(12):2088-2096. doi: 10.3324/haematol.2018.194282.[26]

(5) Suzuki K, Dimopoulos MA, Takezako N, et. al. Daratumumab, lenalidomide, and dexamethasone in East Asian patients with relapsed or refractory multiple myeloma: subgroup analyses of the phase 3 POLLUX study. Blood Cancer J. 2018 May 1;8(4):41. doi: 10.1038/s41408-018-0071-x.[27]

(6) Plesner T, Dimopoulos MA, Oriol A, et al. Health-related quality of life in patients with relapsed or refractory multiple myeloma: treatment with daratumumab, lenalidomide, and dexamethasone in the phase 3 POLLUX trial. Br J Haematol . 2021 Jul;194(1):132-139. doi: 10.1111/bjh.17435.[28]

(7) Kaufman JL, Usmani SZ, San-Miguel J, et. al. Four-Year Follow-up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). Abstract presented at 61st ASH Annual Meeting. Orlando United States. 134(Supplement 1) (pp 1866), 2019.[29]

(8) Bahlis N, Dimopoulos MA, White DJ, et al. Three-Year Follow up of the Phase 3 POLLUX Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). Presented at American Society of Hematology (ASH), 2019.[30]

(9) Dimopoulos MA, San-Miguel J, White D, et. al. Efficacy and safety of daratumumab, lenalidomide, and dexamethasone (D-Rd) in relapsed or refractory multiple myeloma (RRMM): updated subgroup analysis of POLLUX based on cytogenetic risk. Presented at European Hematology Association (EHA), 2019.[31]

The manufacturer used the following outcome measures for the evaluation of additional benefit:

- Primary outcomes: PFS

Secondary outcomes: ORR, OS and HRQoL

3.2.8 Detailed table of clinical trials

A summary of one clinical trial (COLUMBA) that was relevant to the research questions for the main analysis is provided in Table 3-4.

For scenario analysis, three clinical trials were identified (CASTOR, LEPUS and POLLUX) from the searches and the extracted data is reported in Table 3-5. POLLUX study compared addition of daratumumab with lenalidomide and dexamethasone to lenalidomide and dexamethasone, whereas CASTOR and LEPUS studies compared addition of daratumumab with bortezomib and dexamethasone to bortezomib and dexamethasone alone.

3.2.8.1 Main analysis

- Table 3-4 List of literature for main analysis – COLUMBA study

Study name	**COLUMBA study**
Bibliographic information	Mateos MV, Nahi H, Legiec W, Grosicki S, Vorobyev V, Spicka I, Hungria V, Korenkova S, Bahlis N, Flogegard M, Bladé J. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. The Lancet Haematology. 2020 May 1;7(5):e370-80.[7]
Clinicaltrials.gov registry information	NCT03277105
Study sites	Multicenter (147 sites in 18 countries)
Study enrollment period	October 31, 2017 to December 27, 2018
Target population	Recruited patients with RRMM who had received at least three previous lines of therapy and had evidence of response to at least one previous treatment regimen.
Eligibility criteria	• Eligible patients were aged ≥18 years. • Patients had a documented diagnosis of multiple myeloma according to the International Myeloma Working Group

	(IMWG) diagnostic criteria. • Patients with relapsed or refractory multiple myeloma had received at least three previous lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or were double refractory to both a proteasome inhibitor and an immunomodulatory drug. • Patients had evidence of response to at least one previous treatment regimen. • Pretreatment clinical laboratory values during the screening phase were required to show adequate bone marrow, liver, and kidney function. • Women of childbearing potential had to agree to use two methods of birth control at least 4 weeks before first treatment dose and had to have a negative pregnancy test 2 weeks before randomization.
Key exclusion criteria	• Previous treatment with daratumumab or other anti-CD38 therapies. • Anti-myeloma treatment within 2 weeks or five pharmacokinetic half-lives before randomization. • Receipt of an autologous stem cell transplant within 12 weeks before randomization. • Malignancies other than multiple myeloma, unless all treatment of that malignancy had been completed at least 2 years before consent and the patient had no evidence of the disease. • Meningeal involvement of the myeloma. • Chronic obstructive pulmonary disease with a forced expiratory volume in 1 s of less than

	50% of the predicted normal. • Moderate or severe persistent asthma or a history of asthma within the last 2 years. • Clinically significant cardiac disease. • Seropositivity for HIV, hepatitis B, or hepatitis C. • Known allergies to study-relevant compounds and any other conditions that might interfere with the study protocol.
Details of interventional method	• Dara SC group (n=263) Dosing: 1800 mg of daratumumab co-formulated with rHuPH20 2000 U/mL. Patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles).
Details of comparators	• Dara IV group (n=259) Dosing: 16 mg/kg of daratumumab Patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles).
Study design	Randomized, phase 3 trial Randomization was stratified based on baseline bodyweight, previous therapy lines, and myeloma type (IgG vs non-IgG).
Blinding method	Open label
Primary endpoint	Overall response (partial response or better)
Key secondary endpoints	• Proportion of patients with very good partial response or better. • Proportion of patients with complete response or better • Time to response • Duration of response • Progression-free survival • Overall survival

	• Time to next therapy • Patient reported treatment satisfaction • Incidence of infusion-related reactions
Statistical methods	• The Kaplan-Meier method was used to estimate time-to-event distributions. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The infusion-related reaction rate and rates of very good partial response or better were compared between groups using a stratified Cochran-Mantel-Hansel test.
Sample size	• Dara SC group: n=263 • Dara IV group: n=259
Follow-up period	Median, 7.5 months (IQR 6.5–9.3)
Main background factors of subjects	Dara SC group vs Dara IV group • Male, n (%):136 (52) vs 149 (58) • Median age (range), years: 65 (42–84) vs 68 (33–92) • Median weight, kg*: 72.4 (39–130) vs 73 (28.6–138) • Median time since initial diagnosis, years: 6.01 (0.8–21.1) vs 5.36 (0.6–39) • Cytogenetic risk, n (%) ▪ Standard risk: 146 (74) vs 167 (83) ▪ High risk: 52 (26) vs 35 (17)
Efficacy results	Overall Response • An overall response was observed in 41% (n=108/263) patients in the SC group and 37% (n=96/259) in the IV group (RR 1.11, 95% CI 0.89–1.37). PFS • Median PFS was 5.6 vs 6.1 months for SC group vs IV group, respectively (HR 0.99,

	95% CI 0.78–1.26, p=0.93). OS • Six-month survival was 88% (95% CI, 83–91) with SC daratumumab and 83% (95% CI, 78–87) with IV daratumumab. • Follow-up was short and therefore OS data were not mature. Patients with very good partial response • Proportion of patients with very good partial response or better was similar between the SC and IV groups (50 [19%] vs 44 [17%]); OR 1.16, 95% CI 0.73–1.85, p=0.53).
Safety results	IRRs • IRR was significantly lower for SC group vs IV group ▪ Dara SC group: 13%, n=33/260 ▪ Dara IV group: 34%, n=89/258 ▪ OR 0.28, 95% CI 0.18–0.44, p<0.0001 • The most common IRR were chills (5% vs 12% patients), pyrexia (5% vs 3%) and dyspnea (1% vs 7%) in SC group vs IV group, respectively. • With IV group, IRR led to dose interruptions for 79 (31%) patients, one instance of a terminated infusion, decreases in infusion rate in 26 (10%) patients and two treatment discontinuations. • Whereas, with Dara SC, there was no treatment discontinuation, dose interruption or incomplete dose administration. • Median time to onset for IRRs after administration of first dose was longer in the SC group (3.4 h, IQR 1.5–4.4, range 1–47.8) than IV group (1.5 h, 1–1.8, 0–24.5).

	SAEs • Serious adverse events occurred in 26% vs 29% patients in the SC vs IV group • The most common adverse events leading to discontinuation were thrombocytopenia (2 patients in SC group vs 5 in IV group), anemia (2 vs 3) and septic shock (2 vs 3).
Patient-reported outcome	**Satisfaction with therapy [1, 5]:** Cancer Therapy Satisfaction Questionnaire (CTSQ) Patients in the SC group responded more positively to individual components of following parameters vs IV group: • Satisfied with form of cancer therapy • Taking cancer therapy as difficult as expected • Were side effects as expected The Time and Motion survey[5] observed that reduced treatment time which may resulted in increased satisfaction and improved HRQoL.
HCP-reported outcomes[7]	• Time savings for Dara SC compared with Dara IV: ▪ First treatment: 63.8% ▪ Subsequent treatments: 49.5% • Drug preparation time stayed consistent between first and subsequent administrations and was also relatively consistent between the Dara SC and Dara IV formulations. • Drug administration duration was reduced for Dara SC versus Dara IV for primary analysis by: ▪ First treatment: 99% ▪ Subsequent treatments: 98% • Active HCP involvement was reduced for

	Dara SC versus Dara IV for primary analysis by: ▪ First treatment: 96% ▪ Subsequent treatments: 91% • Estimated active HCP time per patient was reduced for Dara SC compared with Dara IV by 50% each for year 1 and year 2. • Estimated patient chair time was reduced for Dara SC compared with Dara IV for primary analysis by 97% each for first and subsequent treatments.
Limitations	• Patients and physicians were not masked to treatment. • Bias cannot be excluded in adverse-event reporting or responses to the modified CTSQ.
Conclusion	• Dara SC was non-inferior to Dara IV in terms of efficacy and had an improved safety profile, especially in IRR. • The time and motion survey showed that Dara SC is associated with substantial reduction in active HCP time, duration of drug administration and patient chair usage compared with Dara IV.

3.2.8.2 Scenario analysis

- Table 3-5 List of literature for scenario analysis

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
Bibliographic information	Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, Mark TM, Qi M, Schecter J, Amin H, Qin X, Deraedt W, Ahmadi T, Spencer A, Sonneveld P; CASTOR Investigators: Daratumumab, Bortezomib, and Dexamethasone for Multiple Myelom, N Engl J Med 2016;375(8):754-66.[8]	Jin Lu, Weijun Fu, Wei Li, Jianda Hu, Gang An, Yafei Wang, Chengcheng Fu, Lijuan Chen, Jie Jin, Xinan Cen, Zheng Ge, Zhen Cai, Ting Niu, Ming Qi, Steven Sun, Xue Gai, Weiping Liu, Wenyu Liu, Xue Yang, Xiaojun Huang. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Chinese Patients with Relapsed or Refractory Multiple Myeloma: Phase 3 LEPUS (MMY3009) Study. Clin Lymphoma Myeloma Leuk. 2021 Sep;21(9):e699-e709. doi: 10.1016/j.clml.2021.04.012.[9]	Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, Plesner T, Yoon SS, Ben Yehuda D, Richardson PG, Goldschmidt H, Reece D, Lisby S, Khokhar NZ, O'Rourke L, Chiu C, Qin X, Guckert M, Ahmadi T, Moreau P; POLLUX Investigators. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375:1319-31.[10]

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
Clinicaltrials.gov registry information	NCT02136134	NCT03234972	NCT02076009
Study sites	Multicenter (115 centers in 16 countries across Europe, North America, South America, and the Asia-Pacific region)	Multicenter (27 sites in China and Taiwan)	Multicenter (135 sites in 18 countries across North America, Europe, and the Asia Pacific region)
Study enrollment period	September 2014 to September 2015	December 24, 2017 to August 6, 2019	June 16, 2014 to July 14, 2015
Target population	Patients had relapsed or refractory multiple myeloma and received one or more lines of previous therapy.	Patients had received at least 1 prior line of therapy for multiple myeloma, had at least a partial response to at least 1 prior multiple myeloma regimen.	Patients had relapsed or refractory multiple myeloma and received one or more lines of previous therapy.
Eligibility criteria	• Patients who had received at least one previous line of therapy for multiple myeloma • Patients had at least a partial response to one	• Patients were ≥18 years of age and had documented multiple myeloma. • Received at least 1 prior line of therapy for multiple myeloma.	• Patients had documented multiple myeloma and measurable disease at screening according to serum or urinary M-protein levels or serum

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	or more of their previous therapies, and had documented progressive disease • At screening, all patients were required to have measurable disease based on assessments of the serum, urine, or both or to have measurable disease as assessed by the serum free light-chain assay	• Had at least a partial response to at least 1 prior multiple myeloma regimen; had documented progressive disease according to International Myeloma Working Group (IMWG) criteria on or after their last regimen. • ECOG PS score of ≤2. • Had measurable disease at screening based on serum M-protein level (≥1 g/dL or 0.5 g/dL for patients with IgA, IgD, IgE, or IgM multiple myeloma), urine M-protein level (≥200 mg/24 hours), or serum Ig free light chain ≥10 mg/dL with abnormal serum Ig kappa lambda free light	free light-chain levels and abnormal serum immunoglobulin free light-chain ratios (kappa: lambda light chains). • Patients had progressive disease according to International Myeloma Working Group (IMWG) criteria during or after the receipt of their last regimen, received and had a response to one or more lines of previous therapy.

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
		chain ratio (for patients without measurable M-protein in serum and urine). • And had any toxicities from prior therapy resolved or stabilized to ≤grade 1.	
Key exclusion criteria	• Neutrophil count of 1000 or less per cubic millimeter, a hemoglobin level of 7.5 g or less per deciliter • Platelet count of less than 75,000 per cubic millimeter, a creatinine clearance of 20 ml or less per minute per 1.73 m^2 of body-surface area • An alanine aminotransferase or	• Patients who had disease refractory to a proteasome inhibitor or were intolerant to bortezomib. • Patients who received prior anti-CD38 therapies. • Patients who received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of treatment, whichever was longer, before randomization.	• Key exclusion criteria were lenalidomide-refractory disease • The discontinuation of previous Lenalidomide treatment owing to adverse events, a neutrophil count of 1.0×109 or less per liter, a hemoglobin level of 7.5 g or less per deciliter, a platelet count of less than 75×109 per liter

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	aspartate aminotransferase level of ≥2.5 times the upper limit of the normal range, and a bilirubin level of ≥1.5 times the upper limit of the normal range • Patient refractory to bortezomib that was refractory to another proteasome inhibitor • Patients had unacceptable side effects from bortezomib • Grade ≥2 peripheral neuropathy or neuropathic pain	• Patients who planned to undergo a stem cell transplantation prior to progression of disease on this study. • Patients who had meningeal involvement of multiple myeloma; grade ≥2 peripheral neuropathy or neuropathic pain; chronic obstructive pulmonary disease with a forced expiratory volume in 1 second <50% of predicted normal; uncontrolled asthma; moderate or severe persistent asthma within the previous 2 years.	• An alanine aminotransferase or aspartate amino transferase level of 2.5 or more times the upper limit of the normal range, • An alkaline phosphatase level of 2.5 or more times the upper limit of the normal range • A bilirubin level of 1.5 or more times the upper limit of the normal range, and a creatinine clearance of less than 30 ml per minute.
Details of interventional	Daratumumab group: Daratumumab + Bortezomib	Daratumumab group: Daratumumab + Bortezomib	Daratumumab group: Daratumumab + Lenalidomide

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
method	+ Dexamethasone (DVd) Dosing: • Daratumumab at a dose of 16 mg per kilogram administered intravenously once per week • Bortezomib administered subcutaneously at 1.3 mg per square meter • Dexamethasone at a dose of 20 mg per cycle (Orally or intravenously) • Patients received daratumumab intravenously once per week (days 1, 8, and 15) during cycles 1 to 3, once every 3 weeks (on day 1) during cycles 4 to 8, and once every 4	and dexamethasone (DVd) Dosing: Daratumumab 16 mg/kg IV was administered weekly during cycles 1 through 3, every 3 weeks during cycles 4 through 8, and every 4 weeks and received up to eight 21-day cycles of bortezomib 1.3 mg/m 2 subcutaneously on days 1, 4, 8, and 11 of each cycle and dexamethasone 20 mg orally or IV on days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. A reduced dose of dexamethasone (20 mg weekly).	+ Dexamethasone (DRd) Dosage: • Daratumumab: 16 mg per kilogram IV administered weekly • Lenalidomide: 25 mg orally • Dexamethasone: 40 mg weekly Patients received daratumumab on days 1, 8, 15, and 22 for 8 weeks during cycles 1 and 2, every 2 weeks (on days 1 and 15) for 16 weeks (cycles 3 through 6), and every 4 weeks. Lenalidomide administered orally on days 1 to 21 of each cycle if the creatinine clearance was more than 60 ml per minute. The dose of dexamethasone

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	weeks until the patient withdrew consent, the disease progressed, or unacceptable toxic effects developed. Patients received Bortezomib on days 1, 4, 8, and 11 of cycles 1 to 8. Dexamethasone administered on days 1, 2, 4, 5, 8, 9, 11, and 12.		was administered at a dose of 20 mg before infusion as prophylaxis for infusion-related reactions and 20 mg was administered the next day.
Details of comparators	Control group: Bortezomib + Dexamethasone (Vd) Dosing: • Bortezomib administered subcutaneously at 1.3 mg per square meter • Dexamethasone at a dose of 20 mg per cycle (orally or intravenously)	Control group: Bortezomib + Dexamethasone (Vd) Dosing: Patients received up to eight 21-day cycles of bortezomib 1.3 mg/m 2 subcutaneously on days 1, 4, 8, and 11 of each cycle and dexamethasone 20 mg orally or IV on days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. A	Control group: Lenalidomide + Dexamethasone (Rd) Dosing: • Lenalidomide: 25 mg orally • Dexamethasone: 40 mg weekly

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
		reduced dose of dexamethasone (20 mg weekly)	
Study design	Randomized, phase 3 trial Randomization was assigned in a 1:1 ratio.	Randomized, phase 3 trial Randomization was assigned in a 2:1 ratio.	Randomized, phase 3 trial Randomization was assigned in a 1:1 ratio
Blinding method	Open label	Open label	Open label
Primary endpoint	Progression-free survival	Progression-free survival	Progression-free survival
Key secondary endpoints	• Time to disease progression • Overall response rate • Proportion of patients who achieved very good partial response or better • Duration of response, the time to response • Overall survival • The time to subsequent antimyeloma treatment was an exploratory	• Overall response (partial response or better) • Very good partial response or better • Median duration of response • Time to response	• Time to disease progression • Overall response rate, rate of very good partial response or better (comprising very good partial, complete, and stringent complete responses) • Rate of complete response or better (comprising complete and stringent complete responses)

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	efficacy end point.		• Percentages of patients with results below the threshold for minimal residual disease, time to response, duration of response, and overall survival
Statistical analysis	• The log-rank test method was used to compared both groups. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The Kaplan–Meier method was used to estimate the distributions. • A stratified Cochran–Mantel–Haenszel chi-	• The Kaplan–Meier method was used to estimate the distributions. • A stratified Cox regression model with treatment as the sole explanatory variable was used to estimate HRs and 95% confidence intervals. • A stratified Cochran–Mantel–Haenszel chi-square test was used to measure treatment differences in the overall	• Stratified log-rank test method was used to compared both groups. • Hazard ratios and 95% confidence intervals were estimated with the use of a Cox regression model, with treatment as the sole explanatory variable. • Cochran–Mantel–Haenszel tests were used to compare overall response rates, rates of very good partial response or better,

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	square test was used to test between-group differences in the overall response rate.	response rate, ≥very good partial response rate, and ≥CR rate.	and other binary end points. Duration of response was assessed by means of the Kaplan–Meier method.
Sample size	• Daratumumab group: n=251 • Control group: n=247	• Daratumumab group: n=141 • Control group: n=70	• Daratumumab group: n=286 • Control group: n=283
Follow-up period	Primary analysis, median: 7.4 months Updated analysis, median: 40 months	Median, 8.2 months	Primary analysis, median: 13.5 months Updated analysis, median: 44.3 months
Main background factors of subjects	Daratumumab group vs control group • Median age (range), years: 64 (30–88) vs 64 (33–85) • Median time since initial diagnosis, years: 3.87 (0.7–20.7) vs 3.72 (0.6–18.6)	Daratumumab group vs control group • Male, n (%): 85 (60.3) vs 42 (60.0) • Median age (range), years: 61.0 (28-79) vs 61.0 (43-82) • Median time since initial diagnosis, years: 3.53	Daratumumab group vs control group • Median age (range), years: 65 (34–89) vs 65 (42–87) • Median time since initial diagnosis, years: 3.5 (0.4–27.0) vs 4.0 (0.4–21.7) • Cytogenetic risk, n/n (%)

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	• Median no. of previous lines of therapy (range): 2 (1–9) vs 2 (1–10) • Cytogenetic risk, n (%) ▪ Standard risk: 140/181 (77.3) vs 137/174 (78.7) ▪ High risk: 41/181 (22.7) vs 37/174 (21.3)	(0.6-11.5) vs 3.45 (0.8-14.1) • Median no. of previous lines of therapy (range): 2 (1-11) vs 2 (1-7) • Cytogenetic risk, n (%) ▪ Standard risk: 92 (66.7) vs 41 (60.3) ▪ High risk: 46 (33.3) vs 27 (39.7)	▪ Standard risk: 193/228 (84.6) vs 176/211 (83.4) ▪ High risk: 35/228 (15.4) vs 35/211 (16.6)
Efficacy results	**Primary analysis[2]** Overall response • The overall response rate was 82.9% in the daratumumab group and 63.2% in the control group (p<0.001). PFS • The 12-month rate of PFS rate was 60.7% (95% CI, 51.2-69.0) in	**Primary analysis [3]** Overall Response An overall response was observed in 82.5% (n=113/137) patients in the D-Vd and 65.1% (n=41/63) in Vd (p= 0.00527). • >CR or better 32.8% (n=45/137) vs 11.1% (n=7/63); p=000.79. • VGPR or better	**Primary analysis[4]** Overall Response • The overall response rate was 92.9% in Daratumumab group vs. 76.4% in the control group (p<0.001). PFS • Median PFS was not reached in Daratumumab group compared with 18.4

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	the daratumumab group as compared with 26.9% (95% CI, 17.1-37.5) in the control group. OS • Remained immature at the time of primary analysis. Partial and complete response • Partial response or better n=142 (59.2% vs. 29.1%, and complete response or better n=68 (19.2% vs. 9.0%, p<0.001) **Exploratory, post hoc, secondary analysis[16]** Median follow-up: 19.4 months PFS	65%(n=89/137) vs 33.3% (n=21/63); p=0.0002 **Subgroup analysis** • Patients with 1 prior line of therapy: 90.2% vs. 66.7%; OR, 4.63; 95% CI, 1.11-19.19. • Patients with prior bortezomib treatment: 81.1% vs. 62.0%; OR, 2.64; 95% CI, 1.24-5.58. • The ORR was higher with DVd versus Vd in the standard-risk cytogenetic abnormalities subgroup (85.6% vs. 57.9%; OR, 4.31; 95% CI, 1.80-10.30). • The ORRs were similar with DVd and Vd in the high-risk cytogenetic	months in the control group (HR 0.41; 95% CI 0.26-0.66; p<0.001). • The Kaplan–Meier PFS rate at 12 months was 83.2% (95% CI, 78.3-87.2) in the daratumumab group and 60.1% (95% CI, 54.0-65.7) in the control group. OS • Kaplan–Meier rate of overall survival at 12 months was 92.1% (95% CI, 88.2-94.7) in the daratumumab group and 86.8% (95% CI, 82.2-90.3) in the control group Patients with very good partial response • Partial response or better response (43.1% vs.

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	• Daratumumab group significantly prolonged PFS as compared to control group (16.7 vs 7.1 months; HR, 0.31; 95% CI, 0.24-0.39; p<0.0001) ORR • ORR was significantly improved with DVd versus Vd (83.8% versus 63.2%; p<0.0001), including higher rates of stringent complete response (8.8% vs 2.6%), CR or better (28.8% vs 9.8%; p<0.0001), and very good partial response or better (62.1% vs 29.1%; p<0.0001).	abnormality's subgroup (75.0% for both groups; OR, 1.00; 95% CI, 0.32-3.15). **PFS** ITT population • Median PFS was NR vs 6.3 months; HR 0.28; 95% CI, 0.17-0.47; p<0.00001 for DVd vs Vd, respectively. • The estimated 12-month PFS rate was 62.4% with DVd versus 24.2% with Vd. • The median time to disease progression was significantly prolonged with DVd versus Vd (median, NR vs. 6.5 months; HR, 0.26; 95% CI, 0.15-0.46; p<0.00001.	19.2%, p<0.001). **Updated exploratory, post hoc, secondary subgroup analyses[11]** Median follow-up: 25.4 months • PFS: Daratumumab group improved PFS compared with control group (median not reached vs. 17.5 months; HR, 0.41; 95% CI, 0.31-0.53; p<0.0001). • ORR: The overall response rate was 92.9% vs 76.4%, and 51.2% vs 21.0% achieved a complete response or better, respectively (both p<0.0001) and deeper responses, including complete response or

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	OS • Remained immature at the time of secondary analysis. **Updated three-year follow-up data[18]** Median follow-up: 40 months • PFS was significantly prolonged for patients receiving daratumumab versus control group (median, 16.7 months vs. 7.1 months; HR, 0.31; 95% CI, 0.25-0.40; p<0.0001). PFS benefit was maintained across patient subgroups, including patient age and cytogenetic risk status. • ORR was significantly	**Subgroup analysis[9]** • Patients with 1 prior line of therapy: Median PFS was NR vs 6.3 months; HR 0.16; 95% CI, 0.06-0.47 for DVd vs Vd, respectively. • With prior bortezomib treatment: Median PFS was NR vs 5.0 months; HR 0.31; 95% CI, 0.19-0.51 for DVd vs Vd, respectively. • High cytogenetic risk: Median PFS was 10.9 months vs 6.3 months; HR, 0.36; 95% CI, 0.18-0.75 for DVd vs Vd, respectively. **OS** • The estimated 12-month	better (56.6 vs 23.2%; p<0.0001). • OS: Data was immature • Subgroup analyses determined that the clinical benefit of daratumumab was maintained in patients regardless of cytogenetic risk status prior lines of therapy received, prior treatment exposure (thalidomide or lenalidomide), or time since last therapy. **Extended follow-up[24]** Median follow-up: 44.3 months • PFS: Daratumumab group significantly prolonged PFS compared with control group (median, 44.5 vs

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	improved with daratumumab group vs control group (85% vs 63%). • OS was not reached. **Subgroup analysis based on cytogenetic risk status[20]** Median follow-up: 40 months **PFS** Daratumumab group prolonged median PFS compared with control group in patients with: • Standard cytogenetic risk (16.6 months vs 6.6 months; HR, 0.26; 95% CI, 0.19–0.37; p=0.0001) • High cytogenetic risk (12.6 vs 6.2 months;	OS rate was 87.8% with DVd versus 68.2% with Vd.	17.5 months; HR, 0.44; 95% CI, 0.35–0.55; p<0.0001). • ORR: Significant improvement was observed in Daratumumab group compared with control group (92.9 vs 76.4%; p<0.0001). **Cytogenetic subgroup analysis[25]** Median follow-up: 44.3 months • PFS: Daratumumab group prolonged PFS vs control group in patients with standard cytogenetic risk (median, not estimable vs 18.6 months; HR, 0.43; 95% CI, 0.32–0.57; p< 0.0001) and high cytogenetic risk (median,

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	HR, 0.41; 95% CI, 0.21–0.83; p=0.0106) **ORR** Higher overall response rate was achieved with Daratumumab group vs control group: • Standard risk: 84% vs 62%, p<0.0001 • High risk: 85% vs 56%, p=0.051		26.8 months vs 8.3 months; HR, 0.34; 95% CI, 0.16–0.72; p=0.0035). • ORR: The ORR and rates of VGPR or better and CR or better were higher with daratumumab group compared with control group, regardless of cytogenetic risk status. • OS: Data was immature.
Safety results	**Primary analysis[8]** • Daratumumab group and the control group had at least one adverse event after the start of treatment (98.8% and 95.4%, respectively). • Hematologic adverse events were observed higher rates in the	**Primary analysis[9]** • Patients reported at least 1 TEAE, and grade 3/4 TEAEs were reported in 89.3% of patients in the DVd group and 75.0% of patients in the Vd group. • The incidence of treatment-emergent cytopenias was high with	**Primary analysis[10]** • The rate of infection of grade 3/4 was slightly higher in the daratumumab group than in the control group (28.3% and 22.8%, respectively). • The most common adverse events leading to

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	daratumumab group than in the control group of any grade of thrombocytopenia (58.8% vs. 43.9%), neutropenia (17.7% vs. 9.3%), and lymphopenia (13.2% vs. 3.8%) • Non-hematologic adverse events, the rate of peripheral sensory neuropathy was higher in the daratumumab group than in the control group (47.3% vs. 37.6%). • The rates of grade 3/4 infections and infestations were similar in the two groups (21.4% and 19.0%,	DVd (any grade, 97.1%; grade 3/4, 72.1%) and Vd (any grade, 91.2%; grade 3/4, 58.8%). • Thrombocytopenia (DVd, 51.4%; Vd, 36.8%) and lymphopenia (DVd, 43.6%; Vd, 29.4%) were the two most commonly reported grade 3/4 TEAEs in both treatment groups. • A higher incidence of infections was reported with DVd versus Vd (any grade, 81.4% vs. 63.2%, respectively; grade 3/4, 54.3% vs. 41.2%), primarily attributed to a higher incidence of any grade and grade 3/4 upper respiratory tract infection	death were acute kidney injury (in 0.4% of the patients in the daratumumab group and in 1.1% in the control group), septic shock (in 1.1% and 0.4%, respectively), and pneumonia (in 0.7% in each group). • The percentage of patients with adverse events leading to the discontinuation of treatment was similar in the two groups: 6.7% in the daratumumab group and 7.8% in the control group. SAEs • Serious adverse events

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	respectively), and the rates of bleeding events of any grade were 7.0% in the daratumumab group and 3.8% in the control group. IRRs • Any grade infusion-related reactions associated with daratumumab were reported in 45.3% of the patients. • Infusion-related reactions were mostly limited to grade 1 or 2 events; at least one grade 3 event was reported in 21 patients (8.6%), and no grade 4 events were reported.	(any grade, 37.9% vs. 22.1%; grade 3/4, 13.6% vs. 4.4%) and lung infection (any grade, 37.1%; vs. 27.9%; grade 3/4, 30.0% vs. 22.1%).	were reported in 48.8% of the patients in the daratumumab group and 42.0% in the control group. • Pneumonia was the most common SAE (in 8.1% in daratumumab group and 8.5% in control group). IRRs • The incidence of daratumumab IRRs of any grade was 47.7%, with 92% of the reactions occurring during the first infusion. These reactions were mostly of grade 1 or 2. • The most common infusion-related reactions were cough (8.5% of the

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	• The most common adverse event were dyspnea (10.7%), bronchospasm (9.1%), and cough (7.0%). **Exploratory, post hoc, secondary analysis[19]** Median follow-up: 19.4 months • The safety profile of daratumumab group remained consistent with longer follow up. **Subgroup analysis based on cytogenetic risk status[18]** Median follow-up: 40 months • Safety profile of daratumumab in standard and high cytogenetic risk		patients), dyspnea (8.5%), and vomiting (5.7%). • A total of 15 patients (5.3%) had grade 3 infusion reactions, and no patient had an event of grade 4 or 5. **Updated exploratory, post hoc, secondary subgroup analyses[26]** Median follow-up: 25.4 months • Safety profile remained unchanged from the primary analysis. • The most common treatment-emergent adverse events of any grade included neutropenia, anemia, thrombocytopenia,

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	subgroups was consistent with the overall population of CASTOR. **Updated three-year follow-up data[20]** Median follow-up: 40 months • No new safety concerns were observed compared with previous analyses. • Most common grade 3/4 TEAEs in the daratumumab vs control group were thrombocytopenia (46% vs. 33%), anemia (16% vs. 16%), and pneumonia (10% vs. 10%).		diarrhea, fatigue, upper respiratory tract infection, cough, constipation, muscle spasms, nasopharyngitis, and nausea. • The most common adverse events (≥1%) leading to treatment discontinuation in daratumumab group compared with control group included pneumonia (1.4%vs. 0.7%), pulmonary embolism (0% vs. 1.1%), general physical health deterioration (1.1% vs. 0%), and renal failure (0.4% vs. 1.1%), respectively.

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
			Extended follow-up[24] Median follow-up: 44.3 months • No new safety concerns were reported in either treatment group with longer follow-up. **Cytogenetic subgroup analysis[25]** Median follow-up: 44.3 months • The safety profile of daratumumab group by cytogenetic risk was consistent with the overall population.
Patient-reported outcomes	**Primary analysis[8, 21]** EORTC QLQ-C30 (Daratumumab group n=227 vs control group n=219) • Mean changes from baseline were generally similar between	Not reported	**Primary analysis[28]** EORTC QLQ-C30 • Mean changes from baseline were significantly greater in global health status, physical functioning, and pain

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	treatment groups for GHS, functioning and symptoms, and did not exceed 10 points for either treatment group (meaningful change, 5 months vs. 5.1 months). • Subgroup analyses based on age (<65 years vs. ≥65 years), ECOG performance status (0 or 1 vs. 2) and depth of response (≥VGPR vs. ≥PR) were consistent with the results observed in the overall population. EQ-5D-5L (daratumumab group n=225 vs control group n=216) • Median time to a		scores in the Daratumumab group vs the Control group; however, magnitude of changes was low, suggesting no meaningful impact on HRQoL. • For subgroup analysis, in both treatment groups, changes from baseline were generally in favour of younger patients versus older patients for GHS, emotional, cognitive, and social functioning scores, and pain and fatigue symptom scores. EQ-5D-5L VAS • Mean EQ-5D-5L VAS scores were maintained with treatment in both

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	meaningful change was 5 months for both treatment groups (HR 1.03; 95% CI: 0.79–1.35; p=0.8072). • For subgroup analysis, Subgroup analyses demonstrated stability of baseline EQ-5D-5L VAS scores regardless of age (<65 years vs. ≥65 years) or depth of response (≥VGPR vs. ≥PR). **Exploratory, post hoc, secondary analysis[19]** Median follow-up: 19.4 months • No significant differences in EORTC QLQ-C30 global health status and		DRd and Rd groups. • For subgroup analysis, irrespective of treatment group, changes from baseline in VAS scores generally favoured younger patients, those with an ECOG performance status of 0 or 1, and those with ≥VGPR. **Updated exploratory, post hoc, secondary subgroup analyses[26]** Median follow-up: 25.4 months • No decline in HRQoL measures were observed with the addition of daratumumab.

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	EQ-5D-5L Utility Score and VAS score were observed.		
Limitations	• Incomplete cytogenetic abnormality data. • Cytogenetic testing was performed locally and no per-protocol specific cut-off values were used for defining the presence of genetic abnormalities.	Not reported	• Small sample size with previous exposure to lenalidomide. • PROs were evaluated as secondary endpoints and were not powered to detect differences between treatment groups. • Only a subset of patient samples was collected for central cytogenetic testing.
Conclusion	• DVd group resulted in significantly longer PFS, and overall response than Vd. • The treatment arm has slightly higher rate of	• LEPUS study confirmed that DVd demonstrated similar efficacy and safety in Chinese patients with RRMM compared with the global phase 3 CASTOR	• DRd was associated with a significant PFS benefit ($p<0.001$) and higher rates of overall response ($p<0.001$) compared to Rd. After more than 3

Study name	CASTOR study	LEPUS (MMY3009) study	POLLUX study
	IRRs, of thrombocytopenia and neutropenia than control group. • For HRQoL, no significant between-group differences for the first eight cycles of therapy were observed for both DVd group and Vd group. • After long-term follow-up (8 cycles of therapy), the DVd group reported improvements in quality of life including GHS, pain and VAS scores as compared to baseline, whereas patients in the Vd group did not receive further treatment.	study. • In LEPUS study, DVd demonstrated significant efficacy benefits versus Vd. • The safety profile was generally consistent with that reported in the global CASTOR study.	years of follow-up, daratumumab group continued to demonstrate improved efficacy versus control group (HR, 0.44; 95% CI, 0.35–0.55; p<0.0001). • Daratumumab group was associated with infusion-related reactions and a higher rate of neutropenia than the control group. • The between-group magnitude of changes from baseline in EORTC QLQ-C30 GHS, functional, and symptom scores, and EQ-5D-5L VAS scores were low, therefore suggesting no meaningful impact on HRQoL.

3.3 Evaluation of Additional Benefit

3.3.1 Results of additional benefit assessment

3.3.1.1 Main analysis: Dara SC vs Dara IV based on COLUMBA trial

COLUMBA clinical trial

The results of main evaluation for Dara SC versus Dara IV are presented in Table 3-6 where the reviewer assessed the individual endpoints. Overall survival is not reported as the data was immature.

- Table 3-6 Additional benefit assessment for COLUMBA study

Study population	Relapsed or refractory multiple myeloma
Intervention	Daratumumab SC
Comparator	Daratumumab IV
Outcomes	ORR, PFS, IRR and treatment satisfaction (PRO)
Presence or absence of additional usefulness	No. The evidence showed that Dara SC was non-inferior to Dara IV in terms of efficacy (ORR and PFS). Despite the confirmed difference in IRR (AE) rate and treatment satisfaction between DARA SC and DARA IV, these benefits are difficult to incorporate under the cost effectiveness analysis framework. Although lower IRR may be associated with some utility gain, however, it was not measured in the clinical trial. Similarly, higher treatment satisfaction, shorter duration of drug administration, and shorter patient chair time which may improve patients' utilities were not captured. There is a limitation within the calculation of ICER to incorporate these additional benefits. Besides, DARA SC is associated with substantial reduction in active HCP time which can improve the efficiency of overall patient management.
Data to support judgment	□ Meta-analysis of RCTs ■ Single clinical trial (9 associated publications) □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies

	□ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional usefulness	**Overall response rate** • COLUMBA study suggested the non-inferiority of Dara SC compared with Dara IV for overall response, despite the ORR is slightly higher in DARA SC group (41% vs 37%). Depth of response (very good partial response or better) was similar between the intervention and comparator groups. • Similar overall responses were observed across prespecified subgroups, including bodyweight categories, despite the Dara SC group not receiving a bodyweight-based dose. • Key finding from COLUMBA study was that depth and time to response were not affected by the route of administration. • For Asian and Japanese-only cohorts, similar results were observed. **Progression-free survival** • For global COLUMBA population, PFS was similar between Dara SC and Dara IV groups (5.6 months vs 6.1 months (p=0.93), respectively). • For Asian and Japanese-only cohorts, similar results were observed. **Infusion-related reaction** • Dara SC had significant reduction in IRRs compared with Dara IV (12.7% versus 34.5% (p<0.0001), respectively). **Treatment satisfaction** • Patients in the Dara SC group had more positive perception and greater satisfaction with treatment than those in the Dara IV group. • Modified Cancer Therapy Satisfaction Questionnaire satisfaction with therapy domain score is higher

	with Dara SC group (76.9) versus Dara IV group (70.5). • Regardless of the route of administration, the majority of patients in the Dara SC group (55.7–81.3%) responded that they would “definitely” take their cancer therapy again compared to Dara IV group (49.8–65.1%) • However, patients and physicians were not masked to treatment, performance bias cannot be excluded in responses to the modified CTSQ.[7] **Other:** • Administration time was found to be markedly less for Dara SC (5 minutes) versus Dara IV (7 hours in the first injection and 3-4 hours per injection afterwards). • Dara SC is associated with substantial reduction in active HCP time, duration of drug administration and patient chair usage compared with Dara IV, resulting in increased satisfaction and may result in better quality of life.

- Table 3-7 ORR analysis in COLUMBA study

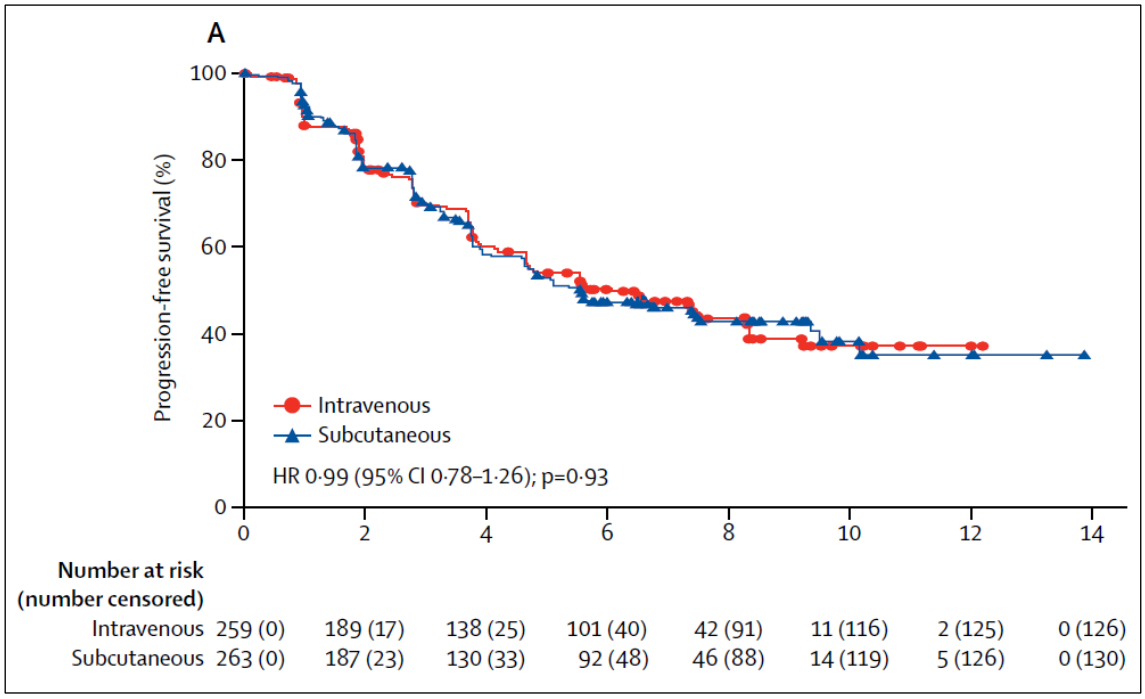
Subgroup	**Dara IV, n/N (%)**	**Dara SC, n/N (%)**	**Relative risk (95% CI)**
Age			
<75 years	70/200 (35.0)	89/216 (41.2)	1.18 (0.92-1.51)
>75 years	26/59 (44.1)	19/47 (40.4)	0.92 (0.58-1.43)
Sex			
Male	54/149 (36.2)	62/136 (45.6)	1.26 (0.95-1.67)
Female	42/110 (38.2)	46/127 (36.2)	0.95 (0.68-1.32)

Region Asia/Pacific Other	 16/52 (30.8) 80/207 (38.6)	 18/43 (41.9) 90/220 (40.9)	 1.36 (0.79-2.34) 1.06 (0.84-1.34)
Weight <65 kg >65-85 kg >85 kg	 35/92 (38.0) 41/105 (39.0) 20/61 (32.8)	 41/94 (43.6) 38/102 (37.3) 29/66 (43.9)	 1.15 (0.81-1.63) 0.95 (0.67-1.35) 1.34 (0.86-2.12)
No of prior lines of therapy <4 >4	 72/175 (41.1) 24/84 (28.6)	 78/174 (44.8) 30/89 (33.7)	 1.09 (0.86-1.39) 1.18 (0.76-1.85)
Cytogenetic risk High risk Standard risk	 11/35 (31.4) 64/167 (38.3)	 20/52 (38.5) 66/146 (45.2)	 1.22 (0.69-2.27) 1.18 (0.91-1.53)
ECOG PS score 0 >1	 36/88 (40.9) 60/171 (35.1)	 26/64 (40.6) 82/199 (41.2)	 0.99 (0.67-1.46) 1.17 (0.91-1.53)

CI: confidence interval; Dara IV: intravenous daratumumab; Dara SC: subcutaneous daratumumab; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ORR: overall response rate

Source: Mateos et al. 2020[7]

- Figure 3-3 Progression-free survival for global COLUMBA population



DARA IV: intravenous daratumumab; DARA SC: subcutaneous daratumumab; HR: hazard ratio; PFS: progression-free survival

Source: Mateos et al. 2020[7]

- Table 3-8 Summary of IRR for global in COLUMBA study

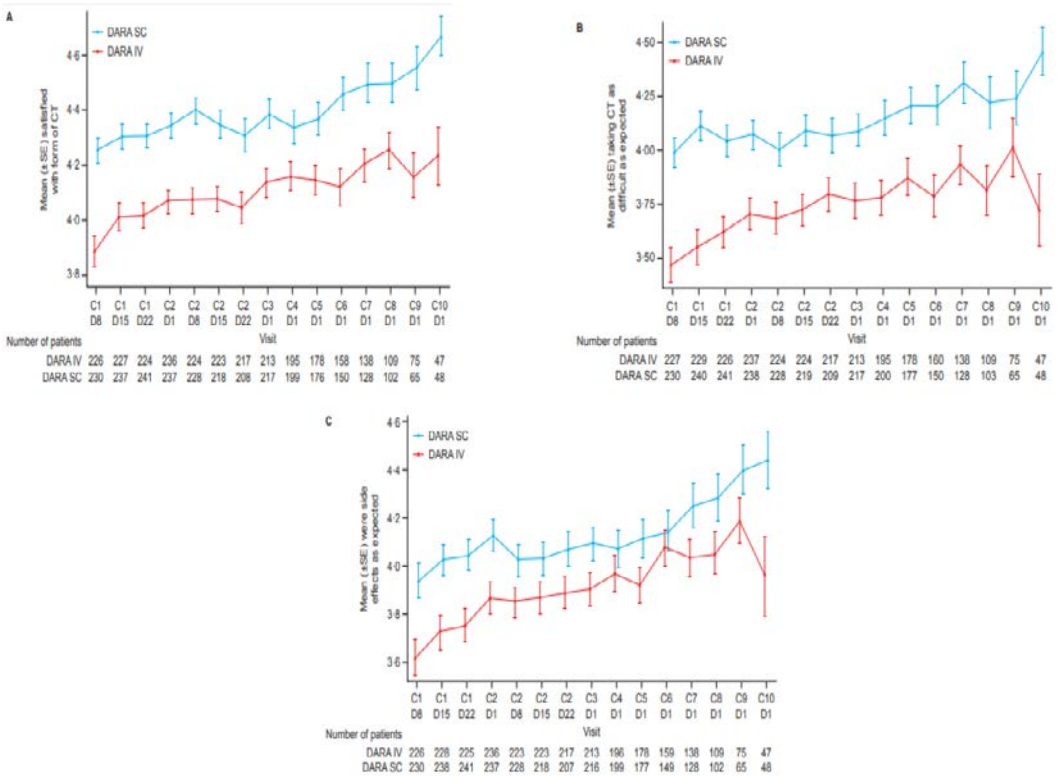
Study group	**Any grade IRRs, n (%)**		**Grade 3 IRRs, n (%)**	
	Dara SC	**Dara IV**	**Dara SC**	**Dara IV**
Global COLUMBA population	33 (12.7)	89 (34.5)	4 (1.5)	14 (5.4)

Dara, daratumumab; IV, intravenous; SC, subcutaneous; IRR, infusion-related reaction

There were no grade4/5 IRR.

Source: Mateos et al. 2020[7]

- Figure 3-4 Modified-CTSQ mean scores for global COLUMBA population for (A) 'Satisfied with Form of Cancer Therapy (Intravenous/Subcutaneous)'; (B) 'Taking Cancer Therapy as Difficult as Expected'; and (C) 'Were Side Effects as Expected'



CTSQ: Cancer Therapy Satisfaction Questionnaire; DARA IV: intravenous daratumumab; DARA SC: subcutaneous daratumumab

Source: Mateos et al. 2020[7]

3.3.1.2 Scenario analysis

As there were no study identified comparing Dara SC with the comparator. The search was broadened to include Dara IV assuming similar efficacy between Dara IV and SC.

DVd vs Vd: The additional benefit result comparing DVd and Vd were confirmed based on two clinical studies (CASTOR and LEPUS). Similar results were observed from both studies.

CASTOR and LEPUS clinical trial

The additional benefit results for CASTOR studies are presented in Table 3-9 where the reviewer assessed the individual endpoints. Phase 3 LEPUS (MMY3009) study was conducted to confirm the efficacy and safety of daratumumab plus bortezomib and dexamethasone in Chinese patients with RRMM compared with the global phase 3 CASTOR study. The additional benefit results for LEPUS study are presented in Table 3-9. Overall survival is not reported for both trials as the data was immature.

- Table 3-9 Additional benefit assessment for CASTOR and LEPUS study

Study Population	Relapsed and/or refractory multiple myeloma
Intervention	Daratumumab + Bortezomib and Dexamethasone (DVd)
Comparative Control	Bortezomib and Dexamethasone (Vd)
Outcomes	PFS, ORR, safety and HRQoL
Presence or absence of additional usefulness	Yes, there is additional benefit comparing DVd* and Vd based on PFS and ORR result in CASTOR and LEPUS study. *There was no study identified comparing Dara SC with the comparator. We first assumed similar efficacy between Dara IV and SC based on COLUMBA study and leverage the result of Dara IV clinical trial.
Data to support judgment	□ Meta-analysis of RCTs ■ 2 clinical trials and 8 associated publications □ Prospective, controlled, observational study □ Indirect comparison of RCTs

	□ Comparison of single-arm studies □ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional usefulness	**Progression-free survival** • Both CASTOR and LEPUS study resulted in significantly longer PFS as compared to Vd alone, with a risk of disease progression or death that was 61.4% (p<0.001) and 72% (p<0.00001) lower, respectively, for the daratumumab group versus the control group.[8, 9] • For CASTOR study, similar PFS results were observed for exploratory post hoc analysis and extended follow-up analyses (median PFS, 16.7 months versus 7.1 months, respectively for both).[18, 19] • Regardless of the cytogenetic risk status subgroup, DVd showed better PFS compared to Vd alone after a median follow-up of more than 3 years (standard risk, 16.6 vs 6.6 months and high risk, 12.6 vs 6.2 months; respectively) in CASTOR study.[20] **Overall response rate** • ORR was significantly improved for DVd group as compared to Vd group for CASTOR study (82.9% vs 63.2% (p<0.001), respectively) and LEPUS study (82.5% vs 65.1%, p=0.00527). • For CASTOR study, the rates of very good partial response or better and complete response or better in the primary analysis, secondary analysis, extended follow-up analysis and cytogenetic risk subgroup analysis (regardless of risk status).[8, 18-20] • For LEPUS study, ORR was higher with DVd as compared to Vd for standard-risk cytogenetic abnormalities subgroup (85.6% versus 57.9%, respectively) and was similar for DVd and Vd in the

	high-risk cytogenetic abnormalities subgroup (75.0% for both groups). **Safety** • DVd was associated with a higher incidence of adverse events in both CASTOR and LEPUS study as compared to Vd alone. • Any grade IRRs associated with DVd group were reported in 45.3% and 37.9% of patients for CASTOR and LEPUS study, respectively. **HRQoL** • For CASTOR study, no significant between-group differences for the first eight cycles of therapy were observed for both DVd and Vd group. • After long-term follow-up (i.e. after 8 cycles of therapy), DVd group reported improvements in quality of life including GHS, pain and VAS scores as compared to baseline, whereas patients in the Vd group did not receive further treatment.

DRd versus Rd: The additional benefit result comparing D-Rd and Rd were confirmed based on POLLUX clinical trial.

POLLUX clinical trial

The additional benefit results for POLLUX studies are presented in Table 3-10, where the reviewer assessed the individual endpoints. Overall survival is not reported as the data was immature.

- Table 3-10 Additional benefit assessment for POLLUX study

Study Population	Relapsed or refractory multiple myeloma
Intervention	Daratumumab + Lenalidomide and Dexamethasone (DRd)
Comparative Control	Lenalidomide and Dexamethasone (Rd)
Outcomes	PFS, ORR, AE and HRQoL

Presence or absence of additional usefulness	Yes, there is additional benefit comparing DRd* and Rd based on PFS and ORR result in POLLUX study. *There was no study identified comparing Dara SC with the comparator. We first assumed similar efficacy between Dara IV and SC based on COLUMBA study and leverage the result of Dara IV clinical trial.
Data to support judgment	□ Meta-analysis of RCTs ■ Single clinical trial and 7 associated publications □ Prospective, controlled, observational study □ Indirect comparison of RCTs □ Comparison of single-arm studies □ No relevant clinical study data □ Other
Reason for judging the presence or absence of additional usefulness	**Progression-free survival** • DRd group reported a 63% lower risk of disease progression or death than Rd group alone (median PFS, NR versus 18.4 months, respectively). • Similar outcome was observed for primary analysis, secondary updated analysis (NR versus 17.5 months, respectively) and long-term follow-up analysis (44.5 vs 17.5 months, respectively) [10, 24, 26] as well as East-Asian population subgroup analysis (NR versus 13.8 months) and cytogenetic subgroup analysis, regardless of cytogenetic risk status (standard risk, NR vs 18.6 months and high risk, 26.8 vs 8.3 months, respectively).[25, 27] **Overall response rate** • DRd was associated with higher rates of overall response as compared to Rd alone (92.9% vs 76.4%, respectively).[10] • Similar outcome was observed for East-Asian population subgroup analysis (90.2% vs 72.1%,

	respectively) and cytogenetic subgroup analysis, regardless of cytogenetic risk status. [25, 27] **Infusion-related reaction** • Incidence of daratumumab any grade IRRs was 47.7%, with 92% of the reactions occurring during the first infusion. **HRQoL** • HRQoL was evaluated as secondary endpoint and was not powered to detect differences between treatment groups. • No meaningful improvements from baseline in HRQoL observed in POLLUX study for both groups. • For subgroup analysis, changes from baseline in HRQoL scores favored younger patients, those with an ECOG performance status of 0 or 1, and those with ≥VGPR, irrespective of treatment group.

4. Details of Analytical Methods

4.1 Analytical Methods

4.1.1 Calculation of cost-effectiveness

1) CMA (Main analysis)

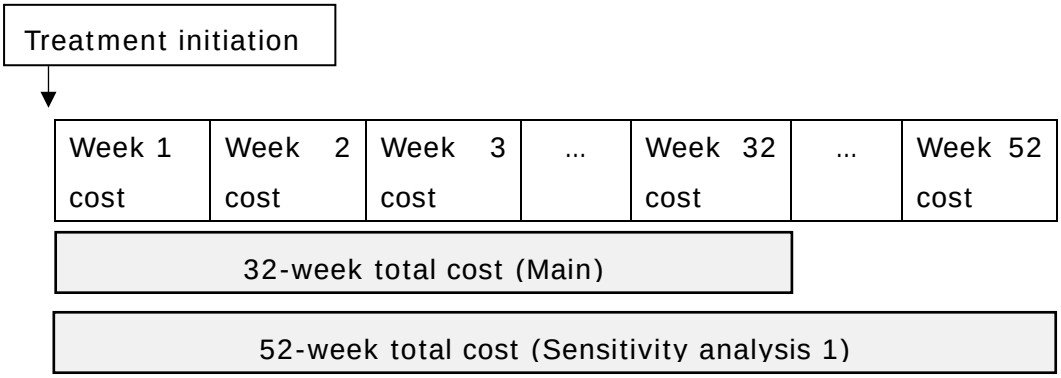
Based on the additional benefit assessment result in section 3. Janssen determined to take a conservative approach and performed a cost minimization analysis as below.

An Excel model was built to calculate weekly direct medical cost including drug, drug administration, hospitalization and IRR (AE) management. Three daratumumab regimens were included, DVMP, DRd and DVd. For each of the regimen, we compare the accumulative direct medical cost between Dara SC (intervention) and DARA IV (comparator). Final results were pooled by the percentage of usage of each regimen in actual clinical practice based on MDV data.

In the main analysis, the duration comparison is set to be 32 weeks based on average daratumumab treatment duration in Japan from MDV data.

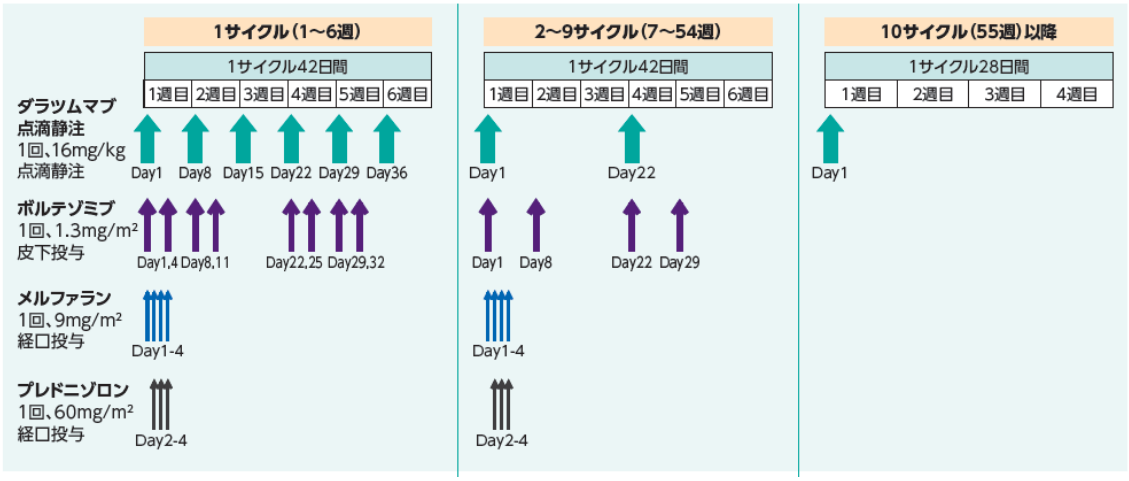
A sensitivity analysis was performed with the duration of 52 weeks [Sensitivity analysis 1]. Another sensitivity analysis was performed assuming [redacted]% of patients receiving DARA SC regimen (due to the improved administration and safety) will not require hospitalization for regimen initiation [Sensitivity analysis 2].

- Figure 4-1 Treatment durations in the analyses

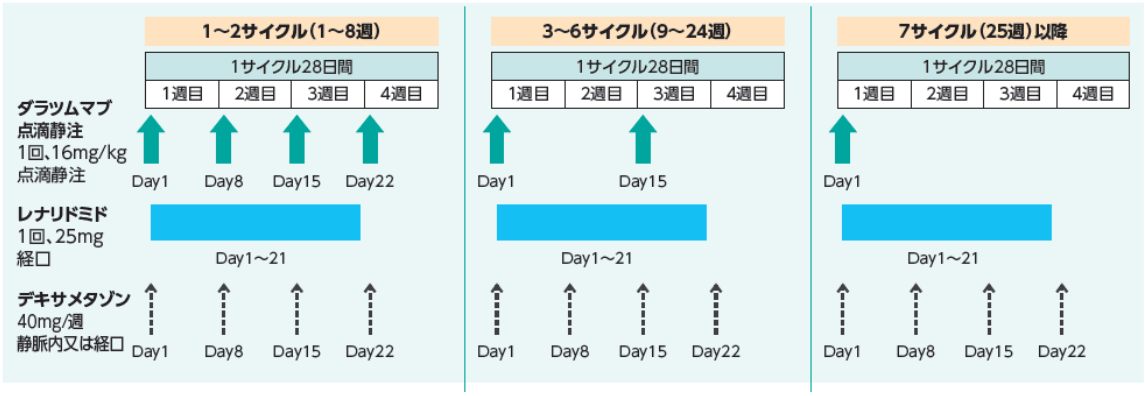


Dosing schedule of each regimen (DVMP, DRd for TIE NDMM, DRD for RRMM and DVd for RRMM) are as following Figure 4-2 to Figure 4-5.

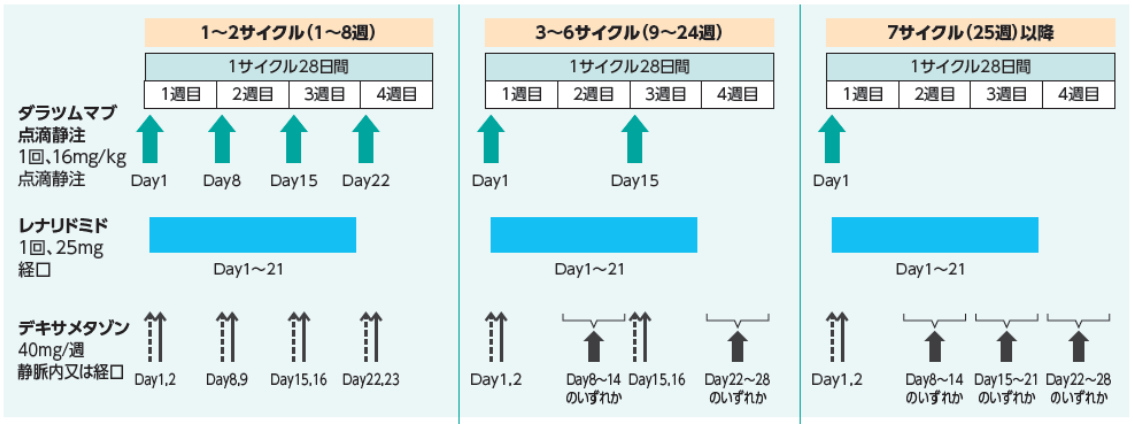
- Figure 4-2 Dosing schedule of DVMP regimen



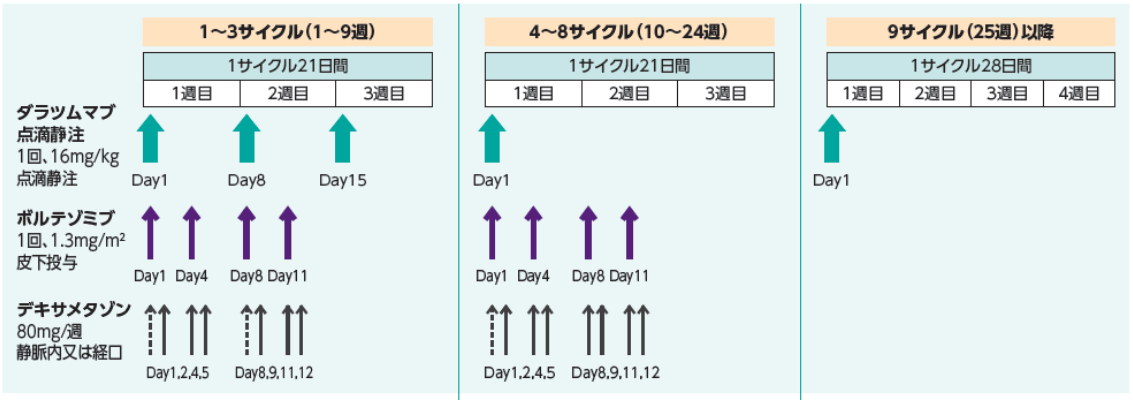
- Figure 4-3 Dosing schedule of DRd regimen for TIE NDMM



- Figure 4-4 Dosing schedule of DRd regimen for RRMM



- Figure 4-5 Dosing schedule of DVd regimen for RRMM



2) Other analysis: Cost difference from HCP time perspective

Based on the result of time in motion survey result [5], the breakdown of the time required from different types of HCPs in the first and a subsequent drug administration visit for DARA SC and DARA IV were acquired. Difference in minutes were calculated between DARA SC and DARA IV. The average hourly wage for the corresponding type of Japan HCP were applied to convert the HCP time into monetary term. Differences were calculated between DRAR SC and DARA IV. The result (HCP time and the value of HCP time) is shown per drug administration patient visit.

3) Other analysis: CUA (Scenario analysis)

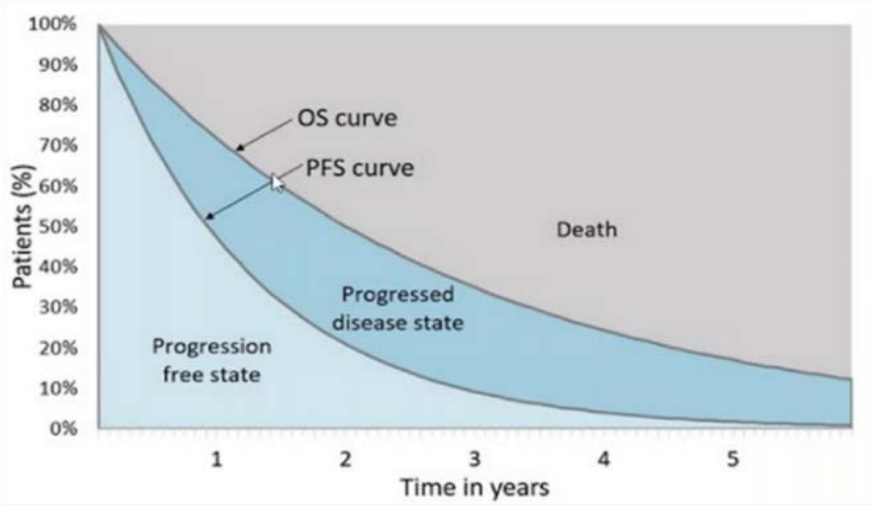
At the request of the expert committee, additional other analysis, cost-utility analyses, were performed for the RRMM indications to assess the cost-effectiveness of DARA SC combination regimens versus non-Dara combination regimens. These cost-utility models were developed in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modeling Practices, and Guideline for cost-effectiveness evaluation in Japan (second edition).

The models assess the incremental cost-effectiveness of DARA SC in combination with Vd or Rd compared with regimen without DARA SC (i.e. DVd vs. Vd and DRd vs. Rd) for the treatment of RRMM.

An excel-based partitioned survival model (PSM) was developed to estimate time and proportion of a cohort of patients in each health state which was estimated using progression free survival (PFS) and overall survival (OS) curves. PSM is a standard and well-accepted approach for oncology models for HTA/payer submissions. The model considered three-health states: pre-progression (or

progression free), post-progression (or progressed disease), and death (Figure 4-6).

- Figure 4-6 Model Structure



Survival was estimated based on the projection of treatment-specific OS curves from the respective daratumumab (DARA) IV clinical trials (MMY3004 [DVd] and MMY3003 [DRd]). It was assumed that DARA SC had the same clinical efficacy as DARA IV. Treatment-specific PFS and OS parametric curves were used to determine health outcomes. To estimate the long-term health outcomes beyond trial periods, multiple parametric functions were fitted to the Kaplan Meier (KM) data for PFS and OS from the two DARA trials with the flexibility to explore all reference curves. The recommended reference curves for base-case and key scenarios were selected based on goodness-of-fit statistics, i.e. Akaike's Information Criteria (AIC), Bayesian Information Criteria (BIC).

Utility values informing the PFS and post-progression survival (PPS) health states as well as disutility values associated with adverse events were based on the data identified in the literature. These were used in the models to derive the quality-adjusted life year (QALY).

The models considered the following cost categories: drug acquisition, drug administration, adverse events, and medical resource uses (including end of life). Drug acquisition and administration costs were estimated by fitting parametric functions to the time-to-treatment discontinuation (TTD) KM data for the daratumumab combinations and comparators which were applied to unit drug costs data informed by Japan standard sources.

Cost outcomes include total and incremental costs and health outcomes are expressed as QALYs gained. The model employs a cost-utility analysis (CUA) calculating incremental cost-utility ratios (ICURs) as incremental costs per incremental QALYs gained.

One way sensitivity analysis (OWSA) is used to test the joint impact of uncertainty in the model parameters on the results.

4.1.2 Assumptions used in the model

1) CMA (Main analysis)

1. Dara IV is a weight-based dosing treatment. the weight for dose calculation is [redacted]Kg based on Japan post-market surveillance data.
2. Drug administration/Hospitalization fee is based on DPC payment schedule. (See Section 4.2.3)
3. MM patients that initiate Dara IV regimens are assumed to admitted to hospital for [redacted] days (MDV database analysis, data cut-off: 2021-May) for drug administration and monitoring side effects. MM patients receiving Dara SC injection are assumed to be hospitalized for [redacted] day as the side effect are less frequent and usually observed in this timeframe.
4. Cost comparison timeframe is set to be 32 weeks based on average duration of daratumumab regimen in Japan (MDV database analysis). The duration of treatment of DARA SC and IV is assumed to be the same based on the non-inferiority result in ORR and PFS from the clinical trial.
5. Since the duration is within 1 year, no discount was applied.
6. Other AE incidence and related costs are assumed to be the same between Dara IV and Dara SC except IRR (grade 3+). IRR cost was estimated based on the AE management guide of the Columba study. It is assumed to be methylprednisolone oral 60 mg per day for an average of [redacted] days.
7. In sensitivity analysis 2, we assumed [redacted]% of patients receiving DARA SC regimen (due to the improved administration and safety) will not require hospitalization for regimen initiation, the rest of patients will follow the original assumptions. All other parameters remain the same with the main analysis.

2) Other analysis: Time and cost difference from HCP time perspective

1. The assumptions in the main CMA analysis were applied when applicable.

2. The HCP time required per administration visit in the publication is assumed to be representative of clinical practice in Japan.
3. When average wage of a specific HCP type information is not available, the average wage of the most similar HCP role is applied.

3) Other analysis: CUA (Scenario analysis)

1. The assumptions in the main CMA analysis were applied in the CUA when applicable.
2. Relative efficacy and safety inputs from the MMY3004 (DVd vs Vd) and MMY3003 (DRd vs Rd) trials are assumed to be representative of the RRMM population in Japan.
3. Dara SC is assumed to have the same efficacy as dara IV in combo with Vd and Rd
4. The cycle length used is 7 days thus, a year is assumed to consist of 52 cycles of 7 days. A half cycle correction was applied.
5. The effect of subsequent treatments is assumed to be implicitly incorporated in the OS curve, as patients in the MMY3004 and MMY3003 studies were allowed to receive other MM treatments upon progression from the randomized treatment.
6. In case the extrapolated PFS and OS curves cross, the model assumes that the percentage of patients who remain on PFS cannot be higher than the percentage of patients who remain on OS.
7. In case the extrapolated OS and the general population mortality curves cross, the model assumes that the percentage of patients who remain alive based on the OS curve cannot be higher than the percentage of patients who remain alive based on the general population mortality curve.
8. Utility values are assumed to be health-state dependent (treatment independent) and constant over time.
9. Patients are assumed to have subsequent treatment costs from disease progression until death. Subsequent treatment costs were derived from MDV, a Japanese claims database.

10. The cumulative probability of IRR (Grade 3+) for each Dara (SC) combination regimen was assumed to equal 1.5% in the absence of the IRR data (cumulative probability based on MMY3012 Dara [SC] arm).
11. The cumulative probabilities of non-IRR adverse events for each dara (SC) combination regimen were assumed to be the same as dara (IV) combination regimen based on MMY3004 (DVd [IV]) and MMY3003 (DRd [SC]) trials.

4.2 Parameters Used in the Analysis

1) CMA (Main analysis)

- Table 4-1 Parameters used for the analysis

Parameter	Main analysis	Sensitivity analysis1	Source
Patient characteristics & Setting			
Body Weight	[redacted] kg		PMS [4]
Proportion of hospitalization for the initial treatment for Dara regimen	[redacted]%		MDV database analysis in Appendix L
Hospitalized days for Dara IV treatment initiation	[redacted] days		MDV database analysis in Appendix L
Hospitalized days for Dara SC treatment initiation	[redacted] day		Assumption
Duration of treatment for Dara regimen	32 weeks	52 weeks	MDV database analysis in Appendix L/ assumption
Efficacy and safety parameter 4.2.1*			
IRR incidence for Dara SC	1.5%		MMY3012 study
IRR incidence for Dara IV	5.4%		MMY3012 study
IRR duration	[redacted] days		MMY3012 study [data on file]

Details of QOL values 4.2.2	Not applicable	
Cost parameters 4.2.3		
Drug cost	See Table 4-3 and 4-4	MHLW list in November 2021 [32][33]
IRR cost per day	[redacted] yen	See Table 4-10 for details
G005 Outpatient chemotherapy fee 1 (1) Injection of antineoplastic drugs II. Age ≥ 15 years	6,000 yen	**
G000 Intradermal, subcutaneous, intramuscular injection fee (per one injection)	200 yen	**
G004: Intravenous infusion 2. to persons other than those specified in 1 (when the daily volume of injection is 500 mL or more)	980 yen	**
G004 Intravenous infusion (per day) 3 Other cases (Only for patients other than hospitalized patients.)	490 yen	**
F400 Prescription Fee 3 in the case of 1 and 2	680 yen	**
DPC cost (per day) (Day 1 - Day 4)	[redacted] yen	**
DPC cost (per day) (Day 5 - Day 14))	[redacted] yen	**
DPC cost (per day) (Day 15 - Day 60)	[redacted] yen	**

*Efficacy is assumed to be the same. Grade3/4 IRR events were included as important safety events in the analysis. The incidence of IRR events and the duration was set following the result of MMY3012.

** For all medical service fees, the revised medical service fees in April 2020, the revised Diagnosis Procedure Combination (DPC) the electronic score table in November 2021, and the Functional Assessment Factor II in April 2020 were used [34] [35] [36].

DPC code: 130040xx99x6xx（Disease name as 'Multiple myeloma, immune system malignant neoplasm', Surgery name as 'None' and Surgery and Procudure, etc.2 as '6') was used.
For the calculation of DPC cost, the coefficients by medical institution was set as follows:
Basic coefficient: [redacted]

The DPC cost was calculated by multiplying the coefficient by medical institution by DPC score which corresponds to the DPC code and the day at the hospitalization, and then converting it into yen.

2) Other analysis: Cost difference from HCP time perspective

Parameters used in the analysis are summarized and presented in Appendix M.

3) Other analysis: CUA (Scenario analysis)

All parameters used in the base-case cost utility analysis are summarized and presented in Appendix A (DVd RRRM model) and Appendix B (DRd RRRM model).

4.2.1 Details of parameters such as efficacy and safety

1) CMA (Main analysis)

See section 4.2, Table 4-1.

2) Other analysis: Cost difference from HCP time perspective

Not applicable

3) Other analysis: CUA (Scenario analysis)

4.2.1.1 Time-to-Event Analysis

Time-to-event analysis was used to model and extrapolate OS and PFS curves based on individual patient data from the clinical trials of each treatment indication.

Following recommendations by the National Institute for Health and Care Excellence (NICE) Decision Support Unit [37] on survival data extrapolation, six parametric distributions were fit to extrapolate time-to-event data and were implemented in the model.

1. Weibull
2. Exponential
3. Log-normal
4. Log-logistic
5. Generalized Gamma
6. Gompertz

The exponential distribution is a one-parameter function and is considered the simplest parametric model. The exponential model is a proportional hazards model, assuming a constant HR over time. The survival function can be expressed as below:

$$S(t) = e^{(-\lambda t)}$$

The Weibull and Gompertz distributions are functions with two parameters — a shape and scale. Therefore, these two distributions are more flexible than the exponential distribution. Both distributions are proportional hazards models. Their survival functions can be expressed as below:

Weibull: $\boldsymbol{S(t) = e^{(-\lambda t^{\gamma})}}$

Gompertz: $\boldsymbol{S(t) = e^{\frac{\lambda}{\theta}(1-e^{(\theta t)})}}$

The log-logistic and log-normal distributions share many similarities. They have a hazard function that can be non-monotonic with respect to time. Therefore, neither of the distributions can be parameterized as a proportional hazards model. Furthermore, due to their functional forms, the log-logistic and log-normal models typically produce long tails in the survivor function. As a result, the clinical validity of log-logistic and log-normal survival models must be carefully assessed. Their survival functions can be expressed as below:

Log-Logistic: $\boldsymbol{S(t) = (1 + e^{\theta} t^{\kappa})^{-1}}$

Log-Normal: $\boldsymbol{S(t)} = 1 - \frac{\Phi(log_t - \mu)}{\sigma}$

where ϕ is the standard normal distribution function

The generalized Gamma distribution is a flexible, three-parameter model. The Weibull, exponential and log-normal distributions are special cases of the generalized Gamma distribution. However, due to its flexibility, the long-term estimations may be influenced by the end of the Kaplan-Meier (KM) curves, which are based on small sample sizes. Therefore, like the log-normal and log-logistic distributions, the clinical validity of the projected survival must be assessed. The survival function can be expressed as below:

Generalized Gamma: $S(t) = 1 - \Gamma_{(\lambda t)^\theta}(\rho)$

where $\Gamma_{(\lambda t)^\theta}(\rho)$ is known as the incomplete gamma function

Recommendations regarding the most appropriate parametric distribution have been made based on graphical assessment, fit statistics Akaike information criterion (AIC)/Bayesian information criterion (BIC) and clinical plausibility of long-term projections. A general rule of thumb is that the distribution with the lowest AIC and BIC values indicate the best fits to the underlying data. Selected time-to-event parameters may be found in 0 (PFS) and 0 (OS).

4.2.1.2 Adverse Events

The model used cumulative probabilities of AEs (infusion-related reaction [IRR] and non-IRRs) that occurred during the observed treatment period in the clinical trials.

In the absence of the IRR data for each Dara (SC) combo regimen, the cumulative probability of IRR (Grade 3+) for each Dara (SC) combo regimen was assumed to equal 1.5%. The cumulative probability was based on the Dara (SC) arm in the MMY3012 study.

For non-IRR AEs, only grade ≥3 AEs occurring in ≥5% of study subjects in any daratumumab arms in the different daratumumab studies were considered. This inclusion criterion has been generally considered appropriate and sufficient to capture AEs that would have a significant impact on resources and costs.

Cumulative probabilities of IRR and non-IRR AEs included in the model during the treatment period available for each regimen are shown are shown in Table 4-2.

- Table 4-2 Adverse Event Rates

Adverse Event	DVd (SC)	Vd	DRd (SC)	Rd
Anemia	[redacted]			
Diarrhea				
Fatigue				
Febrile Neutropenia				
Hypertension				
Infusion-Related Reactions				
Lymphopenia				
Neutropenia				
Peripheral Neuropathy				
Pneumonia				
Source / Rationale	Assumed the same as DVd (IV) based on MMY3004, IRR based on MMY3012	MMY3004	Assumed the same as DRd (IV) based on MMY3003, IRR based on MMY3012	MMY3003
Abbreviations: DRd =daratumumab in combination with lenalidomide and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; IV = intravenous; RRMM = relapsed/refractory multiple myeloma; SC = subcutaneous				

4.2.2 Details of QOL values

1) CMA (Main analysis)

Not applicable.

2) Other analysis: Cost difference from HCP time perspective

Not applicable.

3) Other analysis: CUA (Scenario analysis)

Health state utility values in the base-case scenarios were based on van Agthoven et al. (2004) [38], a commonly cited published study identified in the SLR. Most published RRMM CEAs reference the same data source.

QALYs were calculated as the proportion of patients per health state per cycle multiplied by the utility weights for each health state and proportion of a year represented by the cycle. Utility values used to inform model health states and events in the DRd and DVd models were 0.81 (progression-free) and 0.64 (post-progression).

Utility decrements due to AEs were also calculated based on treatment-specific AE rates and applied as one-time decrements from baseline utility value. Utility decrements used in the RRMM model were [redacted] for DRd (SC) and Rd, [redacted] for DVd (SC), and [redacted] for Vd.

The following methods were used to calculate utility decrement:

1. Adjusted disutility value: duration of AE multiplied by the disutility value per AE
2. Adjusted disutility value multiplied by the cumulative incidence rate per AE
3. Sum of all the calculated incidence rates per treatment regimen

4.2.3 Details of Cost Parameters

Unless otherwise noted, cost parameters values presented were used all analysis.

4.2.3.1 Drug Acquisition Costs

- Table 4-3 Unit Cost of Drug Acquisition

Product name	Ingredient	Specification	Drug price (yen)
Velcade Injection 3 mg	Bortezomib	1 bottle of 3 mg	134,923

Darzalex Intravenous Infusion 100 mg	Daratumumab (Genetical Recombination)	1 bottle of 100 mg 5 mL	52,262
Darzalex Intravenous Infusion 400 mg	Daratumumab (Genetical Recombination)	1 bottle of 400 mg 20 mL solution	187,970
Darzquro Combination Subcutaneous Injection	Daratumumab (Genetical Recombination)/Borhyaluronidase Alfa (Genetical Recombination)	1 bottle of 15 mL	434,209
Decadron Tablet 4 mg	Dexamethasone	1 tablet of 4mg	29.90
Prednisolone tablet	Prednisolone	1 tablet of 5mg	9.80
Alkeran Tablet 2 mg	Melphalan	1 tablet of 2mg	159.70
Revlimid Capsule 5 mg	Lenalidomide Hydrate	1 capsule of 5 mg	8,085.30
Medrol Tablet 4 mg	Methylprednisolone	1 tablet of 4mg	14.8

Based on the unit cost of drug, the unit cost per administration for MM treatment was calculated as follows.

[Unit cost per administration] = [Unit cost of drug] x [Number of doses per administration]

- Table 4-4 Cost per administration used for CMA (MM treatment)

Product name	Dosage	Number of doses per administration	Unit cost per administration (yen)
Velcade Injection 3 mg	2.02 mg (1.3mg×[redacted] *1)*2	1	134,923
Darzalex Intravenous Infusion	884.8 mg (16mg×[redacted]*3)*2	2×400mg + 1×100mg	428,202

Darzquro Combination Subcutaneous Injection	1800mg	1	434,209
Decadron Tablet 4 mg	40 mg (For DRd regimen)	10	299
Decadron Tablet 4 mg	80 mg (For DVd regimen)	20	598
Prednisolone tablet	93 mg (60mg× [redacted] *1)*2	19	186.2
Alkeran Tablet 2 mg	13.95 mg (9mg× [redacted] *1)*2	7	1117.9
Revlimid Capsule 5 mg	25mg	5	40426.5

1 The body surface area for the analysis was set at [redacted] m^2 from the mean height of [redacted] m and the mean weight of [redacted] kg according to the results of the pharmacovigilance plan for Dara IV.

2 Assumed that vials were not reused due to the situation where drugs are used (unused drugs will be discarded).

3 The body weight used in the analysis was set at [redacted] kg based on the mean body weight according to the results of the pharmacovigilance plan for Dara IV.

4.2.3.2 Drug Administration Costs

Administration of IV and SC treatments require an outpatient or inpatient visit that may include nursing and pharmacist preparation time. Therefore, administration costs for IV and SC treatments were included in the model.

The proportion of patients initiating Dara in the hospital setting and duration of hospital stay are shown in Table 4-5.

- Table 4-5 Proportion of Patients Initiating Dara in Hospital and Duration of Hospital Stay

Hospitalization	Daratumumab SC	Source

Proportion of Patients Initiating Dara In Hospital	[redacted]%	MDV database analysis in Appendix L
Duration of Hospital Stay (Days)	[redacted]	Assumption

The hospitalization fee (DPC cost) accounts for costs associated with the hospital bed, care management, and drug acquisition and administration. For the calculation of DPC cost, the coefficients by medical institution were set as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

DPC cost was calculated by multiplying the coefficient by medical institution by DPC score which corresponds to the DPC code and the day at the hospitalization, and then converting it into yen.

Unit costs related to mode of treatment administration are presented in Table 4-1 cost parameters

Proportion of the regimens in clinical practice is shown in Table 4-6.

- Table 4-6 Proportion of regimens in clinical practice (Cost Minimization Analysis)

Regimen (population)	**Proportion**	**Source**
DVMP (TIE NDMM and RRMM)	[redacted]	MDV database analysis in Appendix L
DRd (TIE NDMM)		
DRd		

(RRMM)		
DVd (RRMM)	[redacted]	

Administration costs are based on schedules outlined in Table 4-7. The administration cost is applied per administration and does not vary by length of administration (i.e. an IV administration requiring two hours costs the same as an IV administration requiring seven hours).

- Table 4-7 Dosing Schedules

Regimen	**Treatment**	**Dose per Admin**	**Admin Route**	**Days per Cycles**	**Doses per Cycle**
DRd	Daratumumab (Cycles 1-2)	1800 mg (SC) 16 mg/kg (IV)	SC/IV	28	4
	Daratumumab (Cycles 3-6)	1800 mg (SC) 16 mg/kg (IV)	SC/IV	28	2
	Daratumumab (Cycles 7+)	1800 mg (SC) 16 mg/kg (IV)	SC/IV	28	1
	Lenalidomide (Cycles 1+)	25mg	Oral	28	21
	Dexamethasone (Cycles 1-2)	20mg	Oral	28	8
	Dexamethasone (Cycles 3+)	40mg	Oral	28	4
Rd	Lenalidomide (Cycles 1+)	25mg	Oral	28	21
	Dexamethasone (Cycles 1+)	40mg	Oral	28	4

Regimen	Treatment	Dose per Admin	Admin Route	Days per Cycles	Doses per Cycle
DVd	Daratumumab (Cycles 1-3)	1800 mg (SC) 16 mg/kg (IV)	SC/IV	21	3
	Daratumumab (Cycles 4-8)	1800 mg (SC) 16mg/kg (IV)	SC/IV	21	1
	Daratumumab (Cycles 9+)	1800 mg (SC) 16mg/kg (IV)	SC/IV	28	1
	Bortezomib (Cycles 1-8)	1.3mg/m2	SC/IV	21	4
	Dexamethasone (Cycles 1-8)	20mg	Oral	21	8
Vd	Bortezomib (Cycles 1-8)	1.3mg/m2	SC/IV	21	4
	Dexamethasone (Cycles 1-8)	20mg	Oral	21	8
DVMP	Daratumumab (Cycle 1)	1800 mg (SC) 16 mg/kg (IV)	IV/SC	42.00	6.00
	Daratumumab (Cycles 2-9)	1800 mg (SC) 16 mg/kg (IV)	IV/SC	42.00	2.00
	Daratumumab (Cycles 10+)	1800 mg (SC) 16 mg/kg	IV/SC	28.00	1.00

Regimen	Treatment	Dose per Admin	Admin Route	Days per Cycles	Doses per Cycle
		(IV)			
	Bortezomib (Cycle 1)	1.30mg/m2	IV/SC	42.00	8.00
	Bortezomib (Cycles 2-9)	1.30mg/m2	IV/SC	42.00	4.00
	Melphalan (Cycles 1-9)	9.00mg/m2	Oral	42.00	4.00
	Prednisone (Cycles 1-9)	60.00mg/m2	Oral	42.00	3.00

In clinical practice, bortezomib may be administered via an IV or SC. The proportion of IV administration of bortezomib is reported in Table 4-8.

- Table 4-8 Percent Bortezomib IV Administration

IV Administration % for Bortezomib	Source
[redacted]%	Based on Japan Market Intelligence

Unit cost per administration for MM treatment was calculated as follows:

$$[Unit\ cost\ per\ administration] = [Unit\ cost\ of\ drug]\ x\ [Number\ of\ doses\ per\ administration]$$

Unit costs per administration are presented in Table 4-9.

- Table 4-9 Unit Cost Per Administration

Product Name	Dosage	Number Of Doses Per Administration	Unit Cost Per Administration (Yen)
Velcade Injection 3 mg	[redacted] mg (1.3mg×[redacted] *1)*2	1	134,923.00
Darzalex Intravenous Infusion	[redacted] mg (16mg×[redacted]kg*3)*2	2×400mg + 1×100mg	428,202.00

Product Name	Dosage	Number Of Doses Per Administration	Unit Cost Per Administration (Yen)
Darzquro Combination Subcutaneous Injection	1800mg	1	434,209.00
Decadron Tablet 4 mg	40 mg (For DRd regimen)	10	299.00
Decadron Tablet 4 mg	80 mg (For DVd regimen)	20	598.00
Prednisolone tablet	[redacted] mg (60mg×[redacted] *1)*2	19	186.20
Alkeran Tablet 2 mg	[redacted] mg (9mg×[redacted] *1)*2	7	1,117.90
Revlimid Capsule 5 mg	25mg	5	40,426.50
[1] The body surface area for the analysis was set at [redacted] m^2 from the mean height of [redacted] m and the mean weight of [redacted] kg according to the results of the pharmacovigilance plan for Dara IV. [2] Assumed that vials were not reused due to the situation where drugs are used (unused drugs will be discarded). [3] The body weight used in the analysis was set at [redacted] kg based on the mean body weight according to the results of the pharmacovigilance plan for Dara IV.			

4.2.3.3 Modeling Treatment Duration (Cost Utility Analysis)

Treatment-related costs (drug acquisition and administration) are accrued based on the predicted number of patients who remain on treatment each week (model cycle). The number of patients who remain on treatment over time was estimated based on time to treatment discontinuation (TTD) data from the clinical trials MMY3004 (DVd, RRMM) and MMY3003 (DRd, RRMM) using parametric distribution based on time-to-event analysis. Recommended parametric distributions for the DVd and DRd RRMM models are presented in 0.

Treatment dosing schedules are modelled accurately, using a weekly cycle length

in the model. If a treatment or set of treatments as part of a daratumumab SC regimen are recommended only for up to a fixed duration, drug acquisition and administration costs for those treatments are accrued only up to the maximum fixed duration, unless treatment discontinuation occurs earlier. For example, in the treatment of a patient with RRMM with DVd, the dosing schedule is set such that bortezomib (V) and dexamethasone (d) are only administered for a maximum of up to 24 weeks; hence, their acquisition and administration costs are only accrued for up to 24 weeks, while the acquisition and administration costs of daratumumab (D) are accrued for the time patients remain on treatment, based on the TTD parametric estimator for DVd.

4.2.3.4 Subsequent Treatment Costs (Cost Utility Analysis)

After patients progress on any of the comparators, it is possible to model post-progression treatment costs. Continuing on subsequent treatment after disease progression is a comparator-specific model parameter, the proportion of patients receiving subsequent treatments was available for the two main comparators in the MMY 3003 trial (i.e. DRd and Rd) and MMY 3004 trial (i.e. DVd and Vd).
In the base-case analysis, the proportion of patients continuing on subsequent treatment was 93.3% [39] and 100.0% [39] for DRd (SC) and Rd, respectively, and 82.2% [40] and 100.0% [40] for DVd (SC) and Vd, respectively.

Subsequent treatment costs were derived using the Japanese MDV database (May 2021 data cut) following the protocol outlined on Table L1 (Appendix L). It was assumed that patients would incur the cost for as long as they are in the post-progression survival health state. Annualized drug and administration costs were converted to weekly cost in the model analysis based on the method outlined on Table G1 (Appendix G) and are presented on Table G2 (Appendix G).

4.2.3.5 Adverse Event Costs

The model allows the user to enter individual unit costs of managing infusion-related reaction (IRR) and non-IRR adverse events (AEs). Adverse events related to IRR were based on a micro costing approach derived from the literature [41] and AEs related to non-IRR were obtained from the MDV data base (2021-May cut).

4.2.3.5.1 Infusion-Related Reactions (IRR)

The unit cost for the treatment of IRR as AE was calculated based on the information presented in Table 4-10.

- Table 4-10 Unit Cost Per Administration for IRR Treatment

Product Name	Dosage	Number Of Doses Per Administration	Unit Cost Per Administration (Yen)
Medrol Tablet 4 mg	60 mg/day for 4 days	15 tablets/day × 4 days	888

4.2.3.5.2 All Adverse Events (Cost Utility Analysis)

All AE unit costs used in the model are presented in Table 4-11.

- Table 4-11 RRMM Adverse Event Unit Cost

Adverse Event	Cost Per Event (yen)	Source
Anemia	[redacted]	MDV data (2021-May cut)
Diarrhea		
Fatigue		
Febrile Neutropenia		
Hypertension		
Infusion-Related Reactions		
Lymphopenia		
Neutropenia		
Peripheral Neuropathy		
Pneumonia		
Thrombocytopenia		

An AE cost was applied as a one-time cost at the start of treatment. This approach has been validated and accepted by health economics experts during advisory boards for previous economic models assessing the cost-effectiveness of daratumumab in MM. Additionally, this approach has also been used in these previous economic models of daratumumab in MM.

AE cost per patient per treatment was calculated using the following formula:

$$AE\ Cost\ Per\ Patient = \sum (Cost\ of\ AE\ event_i * Rate\ of\ AE\ event_{ij})$$

Where: i = each AE event presented in 4.2.1.2 and j = treatment

AE costs applied in the model are presented in Table 4-12.

- Table 4-12 Adverse Event Cost Per Patient Used in Base-Case Analysis

Treatment	AE Cost per Patient
DRd (SC)	[redacted]
Rd	
DVd (SC)	
Vd	

4.2.3.6 Medical Resource Utilization (Cost Utility Analysis)

Medical resource utilization (MRU) costs were evaluated for each health state separately in the RRMM models and were derived from the Japanese MDV database (May 2021 data cut). In addition, a one-time end of life cost was estimated and applied to patients who died in the model. The methodology for estimating these MRU costs is presented on Table H1 (Appendix H). Compared to the micro-costing approach, which relies on the frequency of resource use reported by a panel of experts, the Japanese HTA guideline prefers the use of real-world claims database as it reflects the actual clinical practice in Japan at a population level [42]. Annualized MRU costs were converted to weekly cost in the model analysis and presented on Table 4-13.

- Table 0-13. Medical Resource Utilization Costs in RRMM

Category	Annual Costs	Weekly Costs	One-Time Cost
PFS cost	[redacted]		
PPS cost			
End of life cost			

5. Analytical Results

5.1 Results of the Analysis

Analysis performed

Main analysis: Dara SC vs. Dara IV in Multiple Myeloma patients

■Cost Minimization Analysis (Compare costs as equivalent effects)
□Cost-effectiveness analysis (calculate incremental cost-effectiveness ratio)

5.1.1 Incremental cost, effect, and ratio of cost-effectiveness in the base analysis

The results of the cost minimization analysis of Dara SC versus Dara IV are shown below in Table 5-1. In all three combination regimens, Dara SC results in lower total cost compared with Dara IV. The cost saving ranged from ¥443,078 to ¥721,951. Compared with Dara IV, Dara SC reduced total costs by ¥546,091 (weighted average) in the base case.

- Table 5-1 Results of Cost Comparison [base case]

Regimen (population)		Total Cost	Cost difference (SC-IV)	% of Regimen	Total cost difference
DVMP (TIE NDMM and RRMM)	Dara SC	9,682,869 JPY	-718,434 JPY	[redacted]	-546,091 JPY
	Dara IV （Comparator）	10,401,303 JPY			
DRd (TIE NDMM)*	Dara SC	14,340,450 JPY	-443,228 JPY		
	Dara IV （Comparator）	14,783,678 JPY			
DRd (RRMM)*	Dara SC	14,340,600 JPY	-443,078 JPY		
	Dara IV （Comparator）	14,783,678 JPY			
DVd (RRMM)	Dara SC	10,909,818 JPY	-721,951 JPY		
	Dara IV				

Regimen (population)		Total Cost	Cost difference (SC-IV)	% of Regi men	Total cost difference
	（Comparator）	11,631,769 JPY			

*The dosing schedule is slightly different between TIE NDMM and RRMM in DRd regimen, the cost was calculated separately.

5.1.2 Sensitivity analyses

Sensitivity analysis 1 was performed with the duration of 52 weeks. Sensitivity analysis 2 was performed assuming [redacted]% of patients receiving Dara SC regimen (due to the improved administration and safety) will not require hospitalization for regimen initiation.

The results of the sensitivity analysis are shown below. The cost savings of Dara SC versus Dara IV were observed in both sensitivity analysis.

- Table 5-2 Results of Cost Comparison [Sensitivity Analysis 1]

Regimen (population)		Total Cost	Cost difference (SC-IV)	% of Regi men	Total cost difference
DVMP (TIE NDMM and RRMM)	Dara SC	14,497,436 JPY	-723,888 JPY	[redacted]	-550,036 JPY
	Dara IV （Comparator）	15,221,324 JPY			
DRd (TIE NDMM)*	Dara SC	20,766,657 JPY	-447,093 JPY		
	Dara IV （Comparator）	21,213,750 JPY			
DRd (RRMM)*	Dara SC	20,766,807 JPY	-446,943 JPY		
	Dara IV （Comparator）	21,213,750 JPY			
DVd (RRMM)	Dara SC	13,081,863 JPY	-725,816 JPY		
	Dara IV				

Regimen (population)		Total Cost	Cost difference (SC-IV)	% of Regi men	Total cost difference
	（Comparator）	13,807,679 JPY			

*The dosing schedule is slightly different between TIE NDMM and RRMM in DRd regimen, the cost was calculated separately.

- Table 5-3 Results of Cost Comparison [Sensitivity Analysis 2]

Regimen (population)		Total Cost	Cost difference (SC-IV)	% of Regi men	Total cost difference
DVMP (TIE NDMM and RRMM)	Dara SC	9,759,092 JPY	-642,211 JPY	[redacted]	-481,985 JPY
	Dara IV （Comparator）	10,401,303 JPY			
DRd (TIE NDMM)*	Dara SC	14,397,567 JPY	-386,111 JPY		
	Dara IV （Comparator）	14,783,678 JPY			
DRd (RRMM)*	Dara SC	14,397,687 JPY	-385,991 JPY		
	Dara IV （Comparator）	14,783,678 JPY			
DVd (RRMM)	Dara SC	10,985,848 JPY	-645,921 JPY		
	Dara IV （Comparator）	11,631,769 JPY			

*The dosing schedule is slightly different between TIE NDMM and RRMM in DRd regimen, the cost was calculated separately.

5.1.3 Assessing the validity of the analysis

- MM is a plasmacytic malignant tumor which is a type of white cell, and it is essential to be treated by the multidisciplinary treatment at the department of

hematology as centered in close collaboration with other department for its treatment. From this reason, in the setting of the coefficient for DPC code, it is considered as that MM patients was visiting a special function hospital where facilities and systems are established that can provide advanced medical care, especially in the initial stage of treatment with a new drug. This is the rationale of setting the functional assessment factor I and it is considered as appropriate. For the setting of the basic coefficient and the functional assessment factor II, the conservative approach as taking mean value was applied.

- In the setting of the hospitalization rate at the initiation of the treatment, for the management of infusion reaction which was identified as one of the important identified factors for both Dara IV and Dara SC was took into the consideration. In the appropriate use guide, it is recommended as "Patients should be closely monitored for symptoms of infusion reactions during and after treatment with this drug.". In the real world clinical practice, from MDV database analysis, all patients treated with Dara IV were hospitalized at the start of treatment, and the mean length of hospitalization was [redacted] days (mean as [redacted] days and median as [redacted] days). For Dara SC, setting of the hospitalization rate at the initiation of the treatment, the data from MDV database was used. In the case of Dara SC, considering the MMY3012 study results for the time of onset of initial infusion reactions after administration (median as 1,440 mins), it was considered as appropriate to assume that patients were hospitalized for [redacted] day to monitor infusion reactions even after the first dose of this drug. As a sensitivity analysis, it was assumed that [redacted]% of Dara SC patients were not hospitalized at the initiation of the treatment due to convenient administration.
- The treatment duration was set from the mean duration of treatment with Dara IV based on the MDV database analysis. Also in an epidemiological data in Japan [43], the median time to next treatment (TTNT) in MM patients aged 80 years or older was 7.8 months, and the median TTNT was 3.8 months for the period 2016 to 2020 years as the treatment started. This setting was considered as appropriate which took into account that the target population for this analysis includes populations in relatively younger age groups. Since the actual duration of treatment with Dara SC is not yet available, the duration of treatment with Dara SC and Dara IV is assumed to be the same based on the non-inferiority result in ORR and PFS from the clinical trial. In the Australian PBAC evaluation the cost-minimisation analysis comparing the annual cost of Dara SC and Dara

IV was performed and was considered appropriate. Therefore, as a sensitivity analysis, an analysis with a treatment duration of 1 year was also performed.

5.1.4 Interpretation of Analysis Results

Population	Multiple Myeloma
Comparative Control	Dara IV
ICER reference ranges	☐ Usual products ■ Products requiring consideration
Interval considered to have the highest probability of belonging to the ICER	■ Cost reduction or dominant ☐ 5 million yen or less (7.5 million yen or less) ☐ > 5 million yen (> 7.5 million yen) and ≤ 7.5 million yen (≤ 11.25 million yen) ☐ > 7.5 million yen (> 11.25 million yen) and ≤ 10 million yen (≤ 15 million yen) ☐ > 10 million yen (> 15 million yen) ☐ Equivalent (or inferior) efficacy and high cost
Reason for such judgment	It was shown to be cost saving in total costs in the base case as well as the 2 sensitivity analysis that were performed.

5.1.5 Price Adjustment Rate Weight

本剤の追加効能である全身性 AL アミロイドーシスについて、費用対効果評価の対象として指定され現在企業分析を実施中である。本剤の各効能の患者数と患者割合を以下に示す。

本剤の対象集団	患者数（人）	患者割合
MM	6,900	[redacted]
未治療の全身性 AL アミロイドーシス**	[redacted] [44]	
Total	[redacted]	

*悪性腫瘍; **指定難病

5.1.6 Price increases

Not applicable

5.2 Analysis Including Public Nursing Care Expenses and Productivity loss [only if applicable]

Not applicable

5.3 Other Analyses

5.3.1 Other analysis: cost difference from HCP time perspective.

One of the important benefits of Dara SC is to reduce the infusion burden of Dara IV. A Time and Motion study was conducted to quantify this benefit.

5.3.1.1 Result

From the Time and Motion study [5], the breakdown of the time required from different types of HCPs in the first and a subsequent drug administration visit for Dara SC and Dara IV were acquired as following.

- Table 5-4 HCP time per administration visit

	intervention	HCP Time per administration (min)	Time difference per administration (SC-IV)
First infusion/injection	Dara SC	96.3	-169.6 min (-2.8 hours)
	Dara IV (Comparator)	265.9	
Subsequent administration	Dara SC	90.4	-88.8 min (-1.5 hours)
	Dara IV (Comparator)	179.2	

To convert the HCP time into monetary term, the average hourly wage for the corresponding type of Japan HCP were applied. The detail of the analysis was provided in Appendix K.

- Table 5-5 Cost per administration by converting the time to monetary term

	intervention	Cost per the administration	Cost difference (SC-IV)
First infusion/injection	Dara SC	7,928 JPY	-13,211 JPY
	Dara IV (Comparator)	21,139 JPY	

Subsequent administration	Dara SC	7,450 JPY	-6,466 JPY
	Dara IV (Comparator)	13,916 JPY	

5.3.1.2 Interpretation of Analysis Results

The analysis results provided an additional evaluation on HCP time/cost saving that contribute to overall health care system efficiency.

5.3.2 Other analysis: CUA (Scenario analysis)

5.3.2.1 Incremental cost, effect, and ratio of cost-effectiveness

The results of the analysis are summarized and described in detail in the table below for each analysis population.

1) Daratumumab in Combination with Bortezomib and Dexamethasone Subcutaneous Injection (DVd SC) vs Bortezomib and Dexamethasone (Vd) in Patients with RRMM

Total discounted QALYs gained are 3.99 years for DVd (SC) and 2.69 years for Vd. The incremental QALYs gained is 1.30 years, which indicates that DVd (SC) is a more effective treatment than Vd. Total discounted costs are [redacted] yen for DVd (SC) and [redacted] yen for Vd. The incremental cost is [redacted] yen. The ICER of DVd (SC) versus Vd is calculated to be [redacted] yen/QALY (Table 5-6). Details of cost breakdown is presented in Table 5-7.

- Table 5-6 Summary of Analytical Results (RRMM DVd model)

Regimen	Total QALYs	Incremental QALYs	Total Costs (yen)	Incremental Costs (yen)	ICER (yen/QALY)
DVd	3.99	1.30	[redacted]	[redacted]	[redacted]
Vd	2.69		[redacted]		

- Table 5-7 Details of Cost Breakdown (RRMM DVd model)

	Technology Evaluated (yen)	Comparative Control Technology (yen)
Progression-Free		
Drug costs	[redacted]	
Administration costs		
Medical resource use costs		
Adverse event costs		
Post-Progression		
Subsequent treatment drug costs	[redacted]	
Subsequent treatment administration costs		
Medical resource use costs		
End of life costs		
Total Costs		

2) Daratumumab in Combination with Lenalidomide and Dexamethasone Subcutaneous Injection (DRd SC) vs Lenalidomide and Dexamethasone (Rd) in Patients with RRMM

Total discounted QALYs gained are 5.54 years for DRd (SC) and 4.33 years for Rd. The incremental QALYs gained is 1.20 years, which indicates that DRd (SC) is a more effective treatment than Rd. Total discounted costs are [redacted] for DRd (SC) and [redacted] for Rd. The incremental cost is [redacted]. The ICER of DRd (SC) versus Rd is calculated to be [redacted]/QALY (Table 5-8). Details of cost breakdown are presented in Table 5-9.

- Table 5-8 Summary of Analytical Results (RRMM DRd model)

	Total QALYs	Incremental QALYs	Total Costs (yen)	Incremental Costs (yen)	ICER (yen/QALY)
Technology Evaluated	5.54	1.20	[redacted]	[redacted]	[redacted]
Comparative Control Technology	4.33		[redacted]		

- Table 5-9 Details of Cost Breakdown (RRMM DRd model)

	Technology Evaluated (yen)	Comparative Control Technology (yen)
Progression-Free		
Drug Costs	[redacted]	
Administration Costs		
Medical Resource Use Costs		
Adverse Event Costs		
Post-Progression		
Subsequent Treatment Drug Costs	[redacted]	
Subsequent Treatment Administration Costs		
Medical Resource Use Costs		
End Of Life Costs		
Total Costs		

5.3.2.2 One-Way Sensitivity Analysis

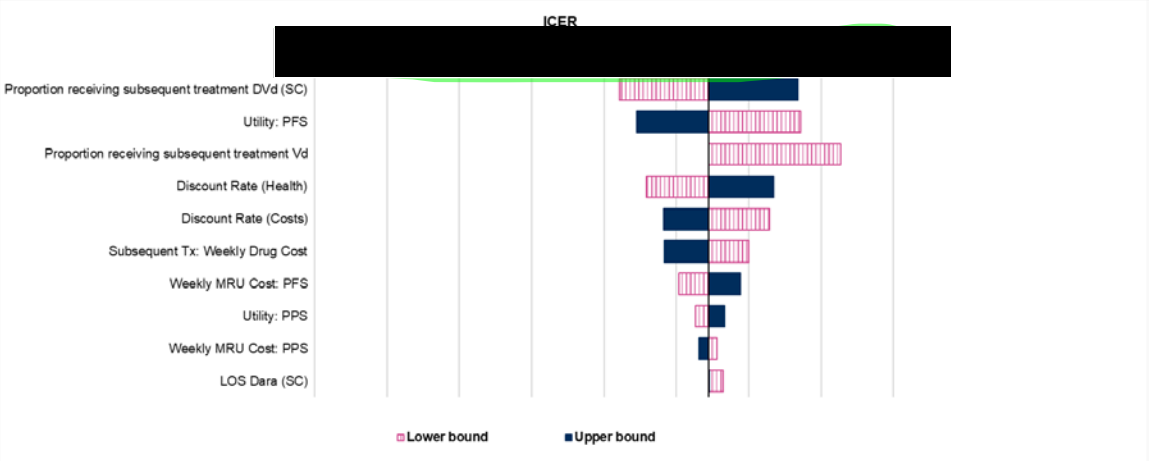
One-way sensitivity analysis (OWSA) was conducted for key model parameters. In the absence of the 95% confidence intervals, an standard error (SE) of 10%

of the base-case estimate was assumed for each parameter, except for discount rates for health and costs which were varied from 0% to 4% per the Japan HTA guidelines.

1) Daratumumab in Combination with Bortezomib and Dexamethasone Subcutaneous Injection (DVd SC) vs Bortezomib and Dexamethasone (Vd) in Patients with RRMM

Table O1 (Appendix O) presents a list of parameters included in the OWSA, their ranges, and the impact on the ICER. Figure 5-1 presents the 10 most influential parameters as a tornado diagram.

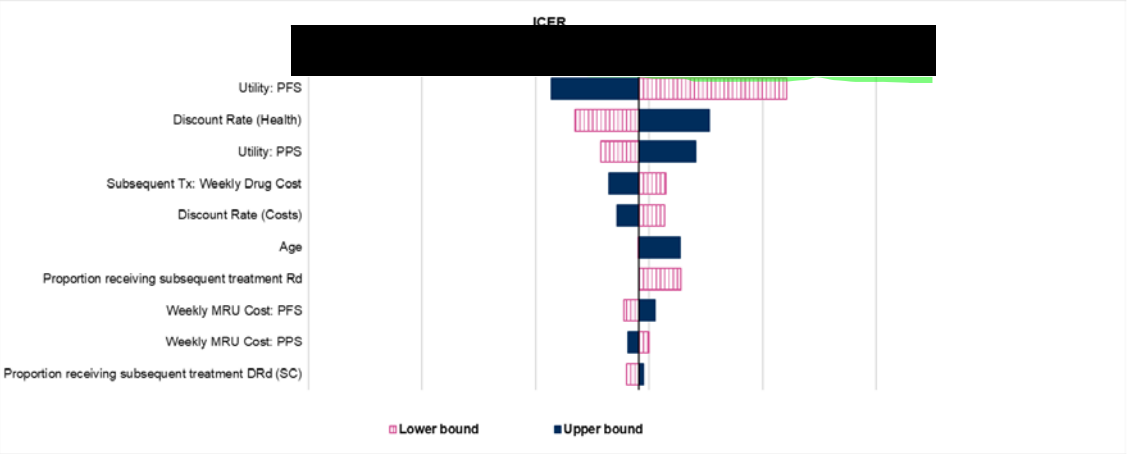
- Figure 5-1 Tornado Diagram of 10 Most Influential Parameters on the ICER of DVd (SC) vs. Vd



2) Daratumumab in Combination with Lenalidomide and Dexamethasone Subcutaneous Injection (DRd SC) vs Lenalidomide and Dexamethasone (Rd) in Patients with RRMM

Table O2 (Appendix O) presents a list of parameters included in the OWSA, their ranges, and the impact on the ICER. Figure 5-2 presents the 10 most influential parameters as a tornado diagram.

- Figure 5-2 Tornado Diagram of 10 Most Influential Parameters on the ICER of DRd (SC) vs. Rd



5.3.2.3 Internal validity

The model was assessed by an external peer reviewer not involved with the original programming. Throughout the validation process a comprehensive and rigorous quality check was fulfilled, including validating the logical structure of the model, mathematical formulas, sequences of calculations, and the values of numbers supplied as model inputs. Unexpected model behavior, implementation and typing errors were all identified by this review. The appropriateness of distributions used in the probabilistic analysis of the model was also checked. Following the validation, correction of identified errors or bugs was incorporated in the revised model.

5.3.2.4 External validity

As external validation, the model's survival predictions were also checked against data observed in the clinical trials used as data sources. The estimation yielded from the model is appropriate in comparison to existing other clinical data.

5.3.2.5 Interpretation of Analysis Results

This analysis only focused on a subset of Multiple Myeloma patients, RRMM, when comparing to Vd and Rd. As it is agreed that the main evaluation focuses on a different population and comparator, this analysis was served as supplementary analysis.

6．再分析用のデータ

使用したソフトウェア	バージョン	ファイル名	提出メディア
Microsoft® Excel® for Microsoft 365 MSO	Version 2108 (Build 14326.20600)	Daratumumab_CMA_JP_MM_v1.0	Email
Microsoft® Excel® for Microsoft 365 MSO	Version 2108 (Build 14326.20600)	Daratumumab_Cost difference from HCP time_v1.0	Email
Microsoft® Excel® for Microsoft 365 MSO	Version 2108 (Build 14326.20600)	Daratumumab_PSM_JP_RRMM_DVd_v5.0	Email
Microsoft® Excel® for Microsoft 365 MSO	Version 2108 (Build 14326.20600)	Daratumumab_PSM_JP_RRMM_DRd_v5.0	Email

7．実施体制

該当せず

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Appendix A: Parameters Used in the Analysis (DVd [SC] vs Vd, Cost Utility Analysis)

- Table A1 RRMM DVd (SC) vs Vd Base-Case Analysis Parameters

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Settings				
Model Cycle Length	1 week	--	--	Based on ISPOR Modeling Good Practices to accurately represent the frequency of clinical events while reducing error
Time Horizon (Years)	30	--	--	Assumed to be a lifetime
Discount Rate	2.0%	--	--	In alignment with Japanese HTA Guidelines
Age (Years)	[redacted]	[redacted]	Normal	Based on MMY3004 trial [8]

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Patient Body Weight (kg) – mean (SD)	[redacted]	[redacted]	Normal	PMS [4]
Patient Height (m) – mean (SD)	[redacted]	[redacted]	Normal	PMS [4]
Patient Body Surface Area	[redacted]	--	--	Calculated based on body weight and height using the DuBois & DuBois algorithm [45]
Intervention	DVd (SC)	--	--	--
Comparators	Vd	--	--	--
Clinical Inputs				
Overall Survival: DVd (SC)	Fitted curve	--	Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
				long-term extrapolation
Overall Survival: Vd	Fitted curve	--	Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Progression-Free Survival: DVd (SC)	Fitted curve	--	Generalized Gamma	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Progression-Free Survival: Vd	KM estimator	--	--	Full KM data is available in the MMY3004 trial
Time-To-Treatment Discontinuation: DVd (SC)	Fitted curve	--	Gompertz	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Time-To-Treatment-Discontinuation: Vd	Fitted curve	--	Lognormal	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
				long-term extrapolation
Subsequent Treatment Specific Probabilities				
DVd (SC)	[redacted]	[redacted]	Normal	Based on MMY 3004 trial – IA3 data cut; Assumed same as DVd (IV) [40]
Vd	[redacted]	[redacted]	Normal	Based on MMY 3004 trial – IA3 data cut [40]
Incidence of AEs Over Time				
Incidence of **Anemia**: DVd (SC)	[redacted]	--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Anemia**: Vd	[redacted]	--	--	Based on MMY3004 trial

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Diarrhea**: DVd (SC)	[redacted]	--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Diarrhea**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Fatigue**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Fatigue**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Febrile Neutropenia**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Febrile Neutropenia**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Hypertension**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Hypertension**: Vd	[redacted]	--	--	Based on MMY3004 trial [8]
Incidence of **Infusion Related Reaction**: DVd (SC)		--	--	Based on MMY3012 trial [7]
Incidence of **Infusion Related Reaction**: Vd		--	--	
Incidence of **Lymphopenia**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Lymphopenia**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Neutropenia**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Neutropenia**: Vd		--	--	Based on MMY3004 trial [8]

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Peripheral Neuropathy**: DVd (SC)	[redacted]	--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Peripheral Neuropathy**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Pneumonia**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Pneumonia**: Vd		--	--	Based on MMY3004 trial [8]
Incidence of **Thrombocytopenia**: DVd (SC)		--	--	Based on MMY3004 trial; Assumed same as DVd (IV) [8]
Incidence of **Thrombocytopenia**: Vd		--	--	Based on MMY3004 trial [8]
Drug Costs				

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Daratumumab (SC)	434,209.00 yen	353,289.77-523,347.54	Gamma	MHLW list in November 2021 [32][33]
Dexamethasone	29.90 yen	24.33-36.04	Gamma	
Bortezomib	134923.00 yen	109,778.74-162,621.27	Gamma	
Drug Administration Costs				
IV Administration % for Bortezomib	[redacted]	[redacted]	Normal	Based on Japan Market Intelligence
Proportion of Patients Initiating DARA (SC) in Hospital			Normal	MDV database analysis in Appendix L
Duration of Hospital Stay (Days) DARA (SC)			Normal	MDV database analysis in Appendix L

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Hospitalization Fee (Day 1 - Day 4)	[redacted]	[redacted]	Gamma	[redacted]
Hospitalization Fee (Day 5 - Day 14)			Gamma	
Hospitalization Fee (Day 15 - Day 21)			Gamma	
DARA (SC) Administration (Outpatient)	200.00 yen	162.73-241.06	Gamma	Ministry of Health Labour and Welfare. Revision of Medical Fee for FY 2020

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Non-DARA IV Administration (Outpatient)	490.00 yen	398.68-590.59	Gamma	(Reiwa 2) [in Japanese] [34]
Non-DARA SC Administration (Outpatient)	200.00 yen	162.73-241.06	Gamma	
Oral Drug Initiation	680.00 yen	553.28-819.60	Gamma	
Annual Subsequent Treatment Drug Costs	[redacted]		Gamma	MDV database analysis in Appendix L
Annual Subsequent Treatment Administration Costs			Gamma	
MRU Costs				
End of Life (One Time Cost)	[redacted]		Gamma	MDV database analysis in Appendix L

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Weekly MRU Cost: PFS	[redacted]		Gamma	
Weekly MRU Cost: PPS			Gamma	
Adverse Event Management Costs				
Anemia	[redacted]		Gamma	MDV database analysis in Appendix L
Diarrhea			Gamma	
Fatigue			Gamma	
Febrile Neutropenia			Gamma	

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Hypertension	[redacted]		Gamma	
Infusion Related Reaction			Gamma	Microcosting approach from the literture 'How to use and concept of new drugs for multiple myeloma'(2017)[In Japanese] [41]
Lymphopenia			Gamma	MDV database analysis in Appendix L
Neutropenia			Gamma	
Peripheral Neuropathy			Gamma	
Pneumonia			Gamma	

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Thrombocytopenia	[redacted]		Gamma	
Utility Inputs				
Pre-Progression (PFS)	0.81	0.69-0.95	Lognormal	van Agthoven, 2004 [38]
Post-Progression (PPS)	0.64	0.56-0.73	Lognormal	van Agthoven, 2004 [38]
Utility Decrement Due to AE: DVd (SC)	[redacted]		Lognormal	See Appendix F for details
Utility Decrement Due to AE: Vd			Lognormal	See Appendix F for details

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CI = Confidence Interval; DRd =daratumumab in combination with lenalidomide and dexamethasone; IV = Intravenous; Kg = Kilograms; M = meters; RRMM = relapsed/refractory multiple myeloma; SC = Subcutaneous; SD = Standard Deviation

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
*For some parameters uncertainty information was not available therefore, 95% confidence intervals (CI) were derived based on the underlying distribution of the parameter and the assumption that the standard error was 10% of the base case value. The lower and upper bound values of the 95% CI were used in one-way sensitivity analysis (OWSA).				

Appendix B: Parameters Used in the Analysis (DRd [SC] vs Rd, Cost Utility Analysis)

- Table B1 RRMM DRd (SC) vs Rd Base-Case Analysis Parameters

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Settings				
Model Cycle Length	1 week	--	--	Based on ISPOR Modeling Good Practices to accurately represent the frequency of clinical events while reducing error
Time Horizon (Years)	30	--	--	Assumed to be a lifetime
Discount Rate	2.0%	--	--	In alignment with Japanese HTA Guidelines
Age (Years)	[redacted]	[redacted]	Normal	Based on MMY3003 trial [10]

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Patient Body Weight (kg) – mean (SD)	[redacted]	[redacted]	Normal	PMS [4]
Patient Height (m) – mean (SD)	[redacted]	[redacted]	Normal	PMS [4]
Patient Body Surface Area	[redacted]	--	--	Calculated based on body weight and height using the DuBois & DuBois algorithm [45]
Intervention	DRd (SC)	--	--	--
Comparator	Rd	--	--	--
Clinical Inputs				
Overall Survival: DRd (SC)	Fitted curve		Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
				long-term extrapolation; Assumed same as DRd (IV) in MMY 3003 trial
Overall Survival: Rd	Fitted curve		Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Progression-Free Survival: DRd (SC)	Fitted curve		Lognormal	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation; Assumed same as DRd (IV) in MMY 3003 trial
Progression-Free Survival: Rd	Fitted curve		Lognormal	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Time-To-Treatment Discontinuation: DRd (SC)	Fitted curve		Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
				long-term extrapolation
Time-To-Treatment-Discontinuation: Rd	Fitted curve		Exponential	Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Subsequent Treatment Specific Probabilities				
DRd (SC)	[redacted]		Normal	Based on MMY 3003 trial – IA3 data cut; Assumed same as DRd (IV) [39]
Rd			Normal	Based on MMY 3003 trial – IA3 data cut [39]
Incidence of AEs Over Time				
Incidence of **Anemia**: DRd (SC)	[redacted]	--	--	Based on MMY3003 trial; Assumed same as DRd

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
				(IV) [10]
Incidence of **Anemia**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]
Incidence of **Diarrhea**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Diarrhea**: Rd		--	--	Based on MMY3003 trial [10]
Incidence of **Fatigue**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Fatigue**: Rd		--	--	Based on MMY3003 trial [10]
Incidence of **Febrile Neutropenia**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Febrile Neutropenia**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]
Incidence of **Hypertension**: DRd (SC)	[redacted]	--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Hypertension**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]
Incidence of **Infusion Related Reaction**: DRd (SC)	[redacted]	--	--	Based on MMY3012 trial [7]
Incidence of **Infusion Related Reaction**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]
Incidence of **Lymphopenia**: DRd (SC)	[redacted]	--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Lymphopenia**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Neutropenia**: DRd (SC)	[redacted]	--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Neutropenia**: Rd		--	--	Based on MMY3003 trial [10]
Incidence of **Peripheral Neuropathy**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Peripheral Neuropathy**: Rd		--	--	Based on MMY3003 trial [10]
Incidence of **Pneumonia**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)
Incidence of **Pneumonia**: Rd		--	--	Based on MMY3003 trial [10]
Incidence of **Thrombocytopenia**: DRd (SC)		--	--	Based on MMY3003 trial [10]; Assumed same as DRd (IV)

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Incidence of **Thrombocytopenia**: Rd	[redacted]	--	--	Based on MMY3003 trial [10]
Drug Costs				
Daratumumab (SC)	434,209.00 yen	353,289.77-523,347.54	Gamma	MHLW list in November 2021 [32][33]
Dexamethasone	29.90 yen	24.33-36.04	Gamma	
Lenalidomide	8,085.30 yen	6,578.52-9,745.13	Gamma	
Drug Administration Costs				
Proportion of Patients Initiating DARA (SC) in Hospital	[redacted]		Normal	MDV database analysis in Appendix L

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Duration of Hospital Stay (Days) DARA (SC)	[redacted]		Normal	Assumption
Hospitalization Fee (Day 1 - Day 4)	[redacted]		Gamma	[redacted]
Hospitalization Fee (Day 5 - Day 14)			Gamma	
Hospitalization Fee (Day 15 - Day 21)			Gamma	
DARA (SC) Administration	200.00 yen	162.73-241.06	Gamma	Ministry of Health Labour and Welfare. Revision of

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
(Outpatient)				Medical Fee for FY 2020 (Reiwa 2) [in Japanese] [34]
Non-DARA IV Administration (Outpatient)	490.00 yen	398.68-590.59	Gamma	
Non-DARA SC Administration (Outpatient)	200.00 yen	162.73-241.06	Gamma	
Oral Drug Initiation	680.00 yen	553.28 - 819.60	Gamma	
Weekly Subsequent Treatment Drug Costs	[redacted]		Gamma	MDV database analysis in Appendix L
Weekly Subsequent Treatment Administration Costs			Gamma	
MRU Costs				

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
End of Life (One Time Cost)	[redacted]		Gamma	MDV database analysis in Appendix L
Weekly MRU Cost: PFS			Gamma	
Weekly MRU Cost: PPS			Gamma	
Adverse Event Management Costs				
Anemia	[redacted]		Gamma	MDV database analysis in Appendix L
Diarrhea			Gamma	
Fatigue			Gamma	

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Febrile Neutropenia	[redacted]	[redacted]	Gamma	
Hypertension	[redacted]	[redacted]	Gamma	
Infusion Related Reaction	[redacted]	[redacted]	Gamma	Micro costing approach from the literature 'How to use and concept of new drugs for multiple myeloma'(2017) [In Japanese] [41]
Lymphopenia	[redacted]	[redacted]	Gamma	MDV database analysis in Appendix L
Neutropenia	[redacted]	[redacted]	Gamma	
Peripheral Neuropathy	[redacted]	[redacted]	Gamma	

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Pneumonia	[redacted]		Gamma	
Thrombocytopenia			Gamma	
Utility Inputs				
Pre-Progression (PFS)	0.81	0.69-0.95	Lognormal	van Agthoven, 2004 [38]
Post-Progression (PPS)	0.64	0.56-0.73	Lognormal	van Agthoven, 2004 [38]
Utility Decrement Due to AE: DRd (SC)	[redacted]		Lognormal	See Appendix F for details
Utility Decrement Due to AE: Rd			Lognormal	See Appendix F for details

Variable Name	Value	95% CI* (If Applicable)	Distribution (If Applicable)	Rationale
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CI = Confidence Interval; DRd =daratumumab in combination with lenalidomide and dexamethasone; IV = Intravenous; Kg = Kilograms; M = meters; RRMM = relapsed/refractory multiple myeloma; SC = Subcutaneous; SD = Standard Deviation *For some parameters uncertainty information was not available therefore, 95% confidence intervals (CI) were derived based on the underlying distribution of the parameter and the assumption that the standard error was 10% of the base case value. The lower and upper bound values of the 95% CI were used in one-way sensitivity analysis (OWSA).				

Appendix C: Time-to-Event Analysis for Progression-Free Survival (PFS)

The recommended distribution to model PFS for each pair of possible comparators is shown in **Table C1**. All relevant data from the fitting exercises, including parameters of the distributions and goodness-of-fit statistics (AIC/BIC) can be found in 0.

- Table C1 Recommended Parametric Distributions for Long-Term Estimation of Progression-Free Survival in the RRMM Models

	Recommended Distribution for PFS	**Source / Rationale**
DVd (SC)	Generalized Gamma	MMY3004 263 OS events data cut (median follow-up [redacted] months); Assumed the same as DVd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Vd	KM estimator	MMY3004 263 OS events data cut (median follow-up [redacted] months); KM estimator used because full follow-up data was available
DRd (SC)	Log-normal	MMY3003 IA3 (median follow-up 32.9 months); Assumed the same as DRd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Rd	Log-normal	MMY3003 IA3 (median follow-up 32.9 months); Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation

	Recommended Distribution for PFS	Source / Rationale
Abbreviations: DRd =daratumumab in combination with lenalidomide and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; IV = intravenous; RRMM = relapsed/refractory multiple myeloma; SC = subcutaneous;		

Appendix D: Time-to-Event Analysis for Overall Survival (OS)

The recommended distribution to model OS for each pair of possible comparators is shown in Table D1. All relevant data from the fitting exercises, including parameters of the distributions and goodness-of-fit statistics (AIC/BIC) can be found in 0.

- Table D1 Recommended Parametric Distributions for Long-Term Estimation of Overall Survival in the RRMM Models

	Recommended Distribution for OS	**Source / Rationale**
DVd (SC)	Exponential	MMY3004 263 OS events data cut (median follow-up [redacted] months); Assumed the same as DVd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Vd	Exponential	MMY3004 263 OS events data cut (median follow-up [redacted] months); Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
DRd (SC)	Exponential	MMY3003 IA3 (median follow-up 32.9 months); Assumed the same as DRd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Rd	Exponential	MMY3003 IA3 (median follow-up 32.9 months); Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation

Abbreviations: DRd =daratumumab in combination with lenalidomide and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; IV = intravenous; RRMM = relapsed/refractory multiple myeloma; SC = subcutaneous

Appendix E: Time-to-Event Analysis for Time-To-Treatment Discontinuation (TTD)

The recommended distribution to model TTD for each pair of possible comparators is shown in Table E1. All relevant data from the fitting exercises, including parameters of the distributions and goodness-of-fit statistics (AIC/BIC) can be found in Appendix K.

- Table E1. Recommended Parametric Distributions for Long-Term Estimation of Time-to-Treatment Discontinuation in the RRMM Models

	Recommended Distribution for TTD	**Source / Rationale**
DVd (SC)	Gompertz	MMY3004 263 OS events data cut (median follow-up [redacted] months); Assumed the same as DVd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Vd	Lognormal	MMY3004 263 OS events data cut (median follow-up [redacted] months); Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
DRd (SC)	Exponential	MMY3003 IA3 (median follow-up 32.9 months); Assumed the same as DRd IV; Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation
Rd	Exponential	MMY3003 IA3 (median follow-up 32.9 months); Based on lowest AIC/BIC goodness-of-fit values and clinical plausibility of long-term extrapolation

	Recommended Distribution for TTD	Source / Rationale
Abbreviations: DRd =daratumumab in combination with lenalidomide and dexamethasone; DVd = daratumumab in combination with bortezomib and dexamethasone; IV = intravenous; RRMM = relapsed/refractory multiple myeloma; SC = subcutaneous		

Appendix F: Details of QOL Values (Disutility Inputs)

- Table F1. Disutility Inputs for RRMM DRd and DVd Models

Adverse Event	Duration of AE (Days)	Disutility	Adjusted Disutility	Source
Febrile Neutropenia	[redacted]			[46]
Neutropenia				[47]
Anemia				[47]
Thrombocytopenia				[47]
Lymphopenia				[47]

Adverse Event	Duration of AE (Days)	Disutility	Adjusted Disutility	Source
Pneumonia	[redacted]			[47]
Diarrhoea				[48]
Fatigue				[48]
Peripheral Neuropathy				[47]
Hypertension				Assume no QoL impact, controlled by medication

Appendix G: Subsequent Treatment Costs in RRMM Models

- Table G1 Protocol for Estimating Subsequent Treatment Costs in RRMM Models

Steps	**Description**
Step 1	Identify the 3rd MM regimen and its first administration date (D1)
Step 2	Identity the end of timeframe – either the end of follow up or death (D2)
Step 3	Calculate the MM-related drug and administration costs between D1 and D2
Step 4	Annualize the MM-related drug and administrations costs by dividing the cost by patient-year

- Table G2 Subsequent Treatment Drug and Administration Costs in RRMM

Category	Annual Costs	Weekly Costs
Drug cost	[redacted]	
Admin cost		

Appendix H: Medical Resource Utilization

- Table H1 Protocol for Estimating Medical Resource Utilization Costs in the RRMM Models

Steps	**Description**
PFS	
Step 1	Identify the first diagnosis of MM in the database, then identify the 1st MM regimen following the diagnosis
Step 2	Identify the 2nd MM regimen and its first administration date (D1)
Step 3	Identify the 3rd MM regimen and its first administration date (D2)
Step 4	Exclude patients who had autologous stem cell transplantation within 12 weeks prior to D1 and patients who had allogeneic stem cell transplantation at any time prior to D1
Step 5	Calculate the non-drug costs between D1 and D2, and exclude the following: drug administration cost, and cost associated with managing AEs
Step 6	Annualize the costs by dividing the cost by patient-year
PPS	
Step 1	Identify the end of timeframe – either the end of follow up or death (D3)
Step 2	Calculate the non-drug costs between D2 and D3, and exclude the following: drug administration cost, cost associated with managing AEs, transplant cost, and end of life cost (MRU costs between 30 days from death and death)

Steps	Description
Step 3	Annualize the costs by dividing the cost by patient-year
End of Life	
Step 1	MRU costs between 30 days from death and death, and exclude the following: drug administration cost, cost associated with managing AEs, and transplant cost

Appendix I: Progression-Free Survival Distribution Parameters (Cost Utility Analysis)

- Table I1 PFS Distribution Parameters (RRMM) – DRd (SC) and DVd (SC)

Distribution	RRMM (DVd SC)					RRMM (DRd SC)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	[redacted]									
Log-normal										
Log-logistic										
Exponential										
Generalised Gamma										
Gompertz										
[1] Gamma value for Gompertz Distribution										

- Table I2 PFS Distribution Parameters (Cost-Utility | RRMM) – Rd and Vd

Distribution	RRMM (Vd)[2]					RRMM (Rd)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	--	--	--	--	--	[redacted]				
Log-normal	--	--	--	--	--					
Log-logistic	--	--	--	--	--					
Exponential	--	--	--	--	--					
Generalised Gamma	--	--	--	--	--					
Gompertz	--	--	--	--	--					

[1] Gamma value for Gompertz Distribution

[2] Kaplan-Meier Estimator used because full follow-up time was available

Appendix J: Overall Survival Distribution Parameters (Cost Utility Analysis)

- Table J1 OS Distribution Parameters (RRMM) – DRd (SC) and DVd (SC)

Distribution	RRMM (DVd SC)					RRMM (DRd SC)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	[redacted]									
Log-normal										
Log-logistic										
Exponential										
Generalised Gamma										
Gompertz										
[1] Gamma value for Gompertz Distribution										

- Table J2 OS Distribution Parameters (Cost-Utility | RRMM) – Rd and Vd

Distribution	RRMM (Vd)					RRMM (Rd)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	[redacted]									
Log-normal										
Log-logistic										
Exponential										
Generalised Gamma										
Gompertz										
[1] Gamma value for Gompertz Distribution										

Appendix K: Time-to-Treatment Discontinuation Distribution Parameters (Cost Utility Analysis)

- Table K1 TTD Distribution Parameters (RRMM) – DRd (SC) and DVd (SC)

Distribution	RRMM (DVd SC)					RRMM (DRd SC)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	[redacted]									
Log-normal										
Log-logistic										
Exponential										
Generalised Gamma										
Gompertz										
[1] Gamma value for Gompertz Distribution										

- Table K2 TTD Distribution Parameters (Cost-Utility | RRMM) – Rd and Vd

Distribution	RRMM (Vd)					RRMM (Rd)				
	Intercept	Scale[1]	Shape	AIC	BIC	Intercept	Scale[1]	Shape	AIC	BIC
Weibull	[redacted]									
Log-normal										
Log-logistic										
Exponential										
Generalised Gamma										
Gompertz										

[1] Gamma value for Gompertz Distribution

Appendix L: MDV database analysis

- Table L1 The methodology for MDV database analysis

Item	Description
Data source	Retrospective claims data obtained from the Medical Data Vision (MDV) database were analyzed from 01 January 2003 to 31 May 2021. The MDV database comprises standardized health-care insurance claims data provided by hospitals in Japan, which is using the Japanese Diagnosis and Procedure Combination (DPC) fixed-payment reimbursement system for over 36 million individuals since the year 2003 and contains about 30 thousand patients with MM.
Study Design and Patient Population	• Adult patients with a diagnosis of MM were considered for this analysis. MM diagnosis was defined as the presence of at least one record with a confirmed MM diagnosis code [redacted]. • Index diagnosis date was defined as the date on which the patient had first record of confirmed MM diagnosis. The baseline period was the 12-month period before the index diagnosis date and the follow-up period consisted of ≥60 days from the index diagnosis date; however, patients who died within this 60-day period were followed for <60 days.
Outcomes evaluated	• Proportion of the treatment regimens for each line and the duration of therapy. • The rate of hospitalization and the duration of the hospitalization in the treatment. • Subsequent treatment drug cost and subsequent treatment administration cost • Annual MRU cost in PFS/PPS • MRU cost in End of life (EOL) • Adverse event cost

Publication	A part of the results was published at the 46th Annual meeting of the Japanese Society of Myeloma [6].

Appendix M: Cost per the administration from the perspective of HCP workload

From the Time and Motion study [5], the breakdown of the first and the subsequent administration time for each HCP was acquired as following.

By multiplying the wage per time for the corresponding Japan HCP role, the cost per the administration from the perspective of HCP workload was calculated as following.

- Table M1 Time required by each HCP role for the administration

HCP role		Dara SC (minutes)	Dara IV (minutes)
All	First infusion/injection	96.3	265.9
	Subsequent administration	90.4	179.2
Pharmacist	First infusion/injection	[redacted]	
	Subsequent administration		
Pharmacy technician	First infusion/injection		
	Subsequent administration		
Transport assistant	First infusion/injection		
	Subsequent administration		
Receptionist	First infusion/injection		
	Subsequent administration		
Auxiliary nurse	First infusion/injection		
	Subsequent administration		
Licensed practical nurse	First infusion/injection		
	Subsequent administration		
Healthcare Support worker	First infusion/injection		
	Subsequent administration		
Registered nurse	First infusion/injection		
	Subsequent administration		
Haematologist	First infusion/injection		
	Subsequent administration		
Phlebotomist	First infusion/injection		
	Subsequent administration		

- Table M2 Wage per time for each HCP role in Japan

HCP role	Hourly wage (JPY)	Wage per minute (JPY)	Source
Pharmacist	[redacted]	[redacted]	Pharmacist [49]
Pharmacy technician	[redacted]	[redacted]	Pharmacist [49]
Transport assistant	[redacted]	[redacted]	General hourly wage [50]
Receptionist	[redacted]	[redacted]	General hourly wage [50]
Auxiliary nurse	[redacted]	[redacted]	Registered nurse [50]
Licensed practical nurse	[redacted]	[redacted]	Registered nurse [50]
Healthcare Support worker	[redacted]	[redacted]	General hourly wage [50]
Registered nurse	[redacted]	[redacted]	Registered nurse [49]
Haematologist	[redacted]	[redacted]	Physician [49]
Phlebotomist	[redacted]	[redacted]	Physician [49]

Appendix N: Literature of Asian and Japanese-only population

- Table N1 List of literature of Asian and Japanese-only population for COLUMBA study

Study name	**COLUMBA study**
Bibliographic information	Iida S, Ishikawa T, Min CK, Kim K, Yeh SP, Usmani SZ, Mateos MV, Nahi H, Heuck C, Qin X, Parasrampuria DA. Subcutaneous daratumumab in Asian patients with heavily pretreated multiple myeloma: subgroup analyses of the noninferiority, phase 3 COLUMBA study. Annals of hematology. 2021 Apr;100(4):1065-77.[12]
Clinicaltrials.gov registry information	NCT03277105
Study sites	Multicenter (147 sites in 18 countries)
Study enrollment period	Oct 31, 2017 to Dec 27, 2018
Target population	Recruited patients with RRMM who had received at least three previous lines of therapy and had evidence of response to at least one previous treatment regimen.
Eligibility criteria	• Eligible patients were aged ≥18 years. • Patients had a documented diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria. • Patients with relapsed or refractory multiple myeloma had received at least three previous lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or were double refractory to both a proteasome inhibitor and an immunomodulatory drug. • Patients had evidence of response to at least one previous treatment regimen.

	• Pretreatment clinical laboratory values during the screening phase were required to show adequate bone marrow, liver, and kidney function. • Women of childbearing potential had to agree to use two methods of birth control at least 4 weeks before first treatment dose and had to have a negative pregnancy test 2 weeks before randomization.
Key exclusion criteria	• Previous treatment with daratumumab or other anti-CD38 therapies. • Anti-myeloma treatment within 2 weeks or five pharmacokinetic half-lives before randomization. • Receipt of an autologous stem cell transplant within 12 weeks before randomization. • Malignancies other than multiple myeloma, unless all treatment of that malignancy had been completed at least 2 years before consent and the patient had no evidence of the disease. • Meningeal involvement of the myeloma. • Chronic obstructive pulmonary disease with a forced expiratory volume in 1 s of less than 50% of the predicted normal. • Moderate or severe persistent asthma or a history of asthma within the last 2 years. • Clinically significant cardiac disease. • Seropositivity for HIV, hepatitis B, or hepatitis C. • Known allergies to study-relevant compounds and any other conditions that might interfere with the study protocol.
Details of interventional	• Dara SC group: n=263 • Asian patients: n=30

method	Dosing: 1800 mg of daratumumab co-formulated with rHuPH20 2000 U/mL. Patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles).
Details of comparators	• Dara IV group: n=259 • Asian patients: n=37 Dosing: 16 mg/kg of daratumumab Patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles).
Study design	• Randomized, phase 3 trial • Randomization was stratified based on baseline bodyweight, previous therapy lines, and myeloma type (IgG vs non-IgG).
Blinding method	Open label
Primary endpoint	Overall response (partial response or better)
Key secondary endpoints	• Proportion of patients with very good partial response or better and complete response or better • Time to response • Duration of response • Progression-free survival • Overall survival • Time to next therapy • Patient reported treatment satisfaction • Incidence of infusion-related reactions
Statistical methods	• The Kaplan-Meier method was used to estimate time-to-event distributions. • Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards regression model. • The infusion-related reaction rate and rates of very good partial response or better were

	compared between groups using a stratified Cochran-Mantel-Hansel test.
Sample size	Dara SC Asian patients (n=30): • Korean n=4 • Taiwanese n=8 • Japanese n=18 Dara IV Asian patients (n=37): • Korean n=7 • Taiwanese n=6 • Japanese n=24
Follow-up period	Median, 7.5 months (IQR 6.5–9.3)

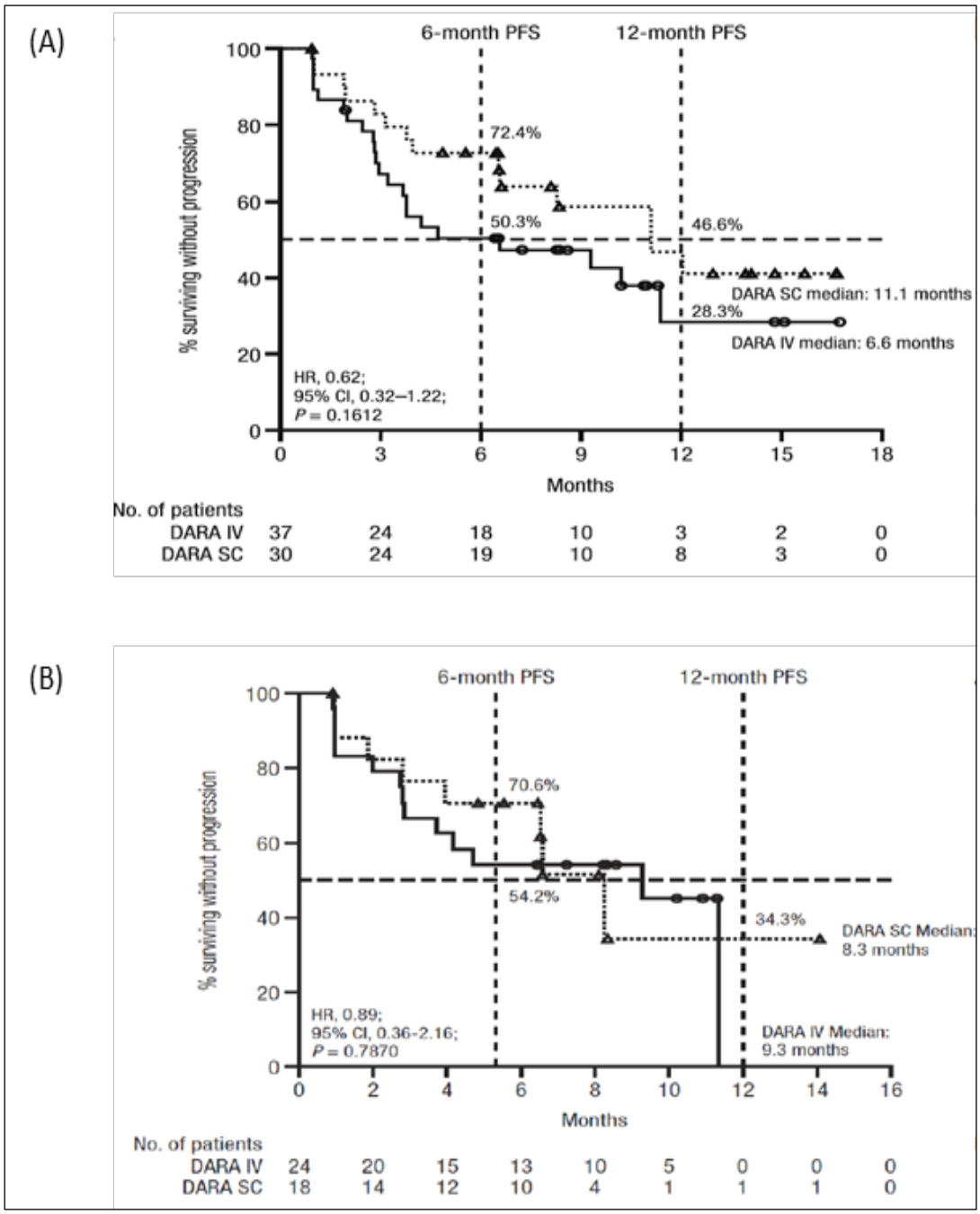
Main background factors of subjects	Dara SC group vs IV group
	• Male, n (%):20 (54.1) vs 15 (50.0)
	• Median age (range), years: 70.0 (33–83) vs 70.5 (48–84)
	• Median weight, kg: 56.7 (32.8–93.0) vs 60.1 (40.5–83.2)
	• Cytogenetic risk, n (%)
	  • Standard risk: 29 (78.4) vs 18 (69.2)
	  • High risk: 8 (21.6) vs 8 (30.8)

Efficacy in Asian population	ORR An overall response was observed in 66.7% (n=20/30) patients in the SC group (median NR, 95% CI 7.39-NE) and 43.2% (n=16/37) in the IV group (median 10.41, 95% CI 8.31-NE) PFS • Median PFS was 11.1 vs 6.6 months for SC group vs IV group, respectively (HR 0.62, 95% CI 0.32–1.22, p=0.16). • 6-month and 12-month PFS rates were 72.4% versus 50.3% and 46.6% versus 28.3%, respectively.
Safety in Asian population	IRR • Dara SC group: 10%, n=3/30

	• Dara IV group: 18.9%, n=7/37 • OR, 0.48; 95% CI, 0.11–2.03; p=0.3120 Grade 3/4 TEAEs • Dara SC group: 53.3% (n=16) • Dara IV group: 56.8% (n=21) SAEs • Dara SC group: 13.3% (n=4) • Dara IV group: 40.5% (n=15)
PRO in Asian population	Patients in the SC group responded more positively to individual components of following parameters vs IV group: • Satisfied with form of cancer therapy • Taking cancer therapy as difficult as expected
Efficacy in Japanese population	ORR An overall response was observed in 61.1% (n=11/18) patients in the SC group (Median- NR, 95% CI 4.53-NE) and 54.2% (n=13/24) in the IV group (median 10.41, 95% CI 8.31-10.41) PFS • Median PFS was 8.3 months with DARA SC versus 9.3 months with DARA IV (HR, 0.89; 95% CI, 0.36–2.16; p= 0.7870) • 6-month and 12-month PFS rates were 70.6% versus 54.2% and 34.3% versus 0%, respectively.
Safety in Japanese population	IRR The IRR rate was the same for patients receiving DARA SC and DARA IV in Japanese cohort. • Dara SC group: 16.7%, n=3/18 • Dara IV group: 16.7%, n=4/24 Grade 3/4 TEAEs • Dara SC group: n=10 (55.6%) • Dara IV group: n=10 (41.7%) The rates of grade 3/4 neutropenia (27.8% for

	DARA SC and 0% for DARA IV, respectively), lymphopenia (16.7% and 8.3%) and leukopenia (11.1% and 4.2%) were higher in the Japanese-only cohort as compared to Asian cohort. Grade 3/4 anemia was reported at a higher rate with DARA SC (22.2%) compared to the global COLUMBA safety population and occurred in no patients receiving DARA IV. SAEs • Dara SC group: n=2 (11.1%) • Dara IV group: n=7 (29.2%)
PRO in Japanese population	Mean scores of CTSQ assessment were similar between the DARA SC and DARA IV groups.
Conclusion	Efficacy and safety of DARA SC in Asian patients and Japanese sub-analysis were generally consistent with those of the global COLUMBA population.

- Figure N1 Progression free survival for (A) Asian and (B) Japanese-only population



Dara: daratumumab; IV: intravenous; PFS: progression-free survival; SC: daratumumab subcutaneous

Source: Iida et al. 2021[12]

- Table N2 List of literature of East Asian (Japanese, Korean, and Taiwanese) population for POLLUX study

Study name	POLLUX study
Bibliographic information	Suzuki K, Dimopoulos MA, Takezako N, Okamoto S, Shinagawa A, Matsumoto M, Kosugi H, Yoon SS, Huang SY, Qin X, Qi M. Daratumumab, lenalidomide, and dexamethasone in East Asian patients with relapsed or refractory multiple myeloma: subgroup analyses of the phase 3 POLLUX study. Blood cancer journal. 2018 May 1;8(4):1-9.[27]
Clinicaltrials.gov registry information	NCT02076009
Study sites	Multicenter
Study enrollment period	Randomized between June 2014 and July 2015, and the clinical cutoff date for this analysis was 7 March 2017.
Target population	Patients had documented multiple myeloma and measurable disease at screening according to serum or urinary M-protein levels and they had received and had a response to one or more lines of previous therapy.
Eligibility criteria	Eligible patients had progressive disease according to International Myeloma Working Group (IMWG) criteria during or after their last regimen and had received and responded to ≥1 line of prior therapy
Key exclusion criteria	• Key exclusion criteria were lenalidomide-refractory disease. • The discontinuation of previous lenalidomide treatment owing to adverse events. • A neutrophil count of 1.0×109 or less per liter. • A hemoglobin level of 7.5 g or less per deciliter. • A platelet count of less than 75×109 per liter. • An alanine aminotransferase or aspartate aminotransferase level of 2.5 or more times

	the upper limit of the normal range. • An alkaline phosphatase level of 2.5 or more times the upper limit of the normal range. • A bilirubin level of 1.5 or more times the upper limit of the normal range, and a creatinine clearance of less than 30 ml per minute.
Details of interventional method	• Daratumumab plus lenalidomide and dexamethasone (DRd): n=286 • East Asian patients: n=52 • Dosing: Lenalidomide: 25 mg orally on Days 1-21 of each 28-day cycle; dexamethasone: 40 mg orally weekly) with daratumumab (16 mg/kg intravenously weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks.
Details of comparators	• Lenalidomide and dexamethasone (Rd): n=283 • East Asian patients: n=44 • Japanese patients: n=15 Dosing: lenalidomide: 25 mg orally on Days 1-21 of each 28-day cycle; dexamethasone: 40 mg orally weekly) without daratumumab (16 mg/kg intravenously weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks.
Study design	Randomized, phase 3 trial
Blinding method	Open label
Primary endpoint	Progression-free survival
Key secondary endpoints	• Overall response (partial response or better) • Proportion of patients with very good partial response or better. • Proportion of patients with complete response or better • Median duration of response

	• Time to response • Overall survival • Health-related Quality of Life
Statistical methods	• Progression-free survival was compared between treatment groups based on a stratified log-rank test. • Hazard ratios and 95% confidence intervals were estimated using a Cox regression model with treatment as the sole explanatory variable. • The Kaplan-Meier method was used to estimate the distributions. • Stratified Cochran-Mantel-Haenszel tests were used to test treatment differences in overall response rate and rates of very good partial response or better and complete response or better.
Sample size	DRd group East-Asian patients: n=52 • Japanese patients: n=21 Rd group East-Asian patients: n=44 • Japanese patients: n=15
Follow-up period	Median (range) • East Asian patients: 24.7 (0.7–30.5) months • Japanese patients: 21.4 (4.4–24.1) months

Main background factors of subjects	East Asian patients (DRd vs Rd group):
	• Male, %: 50 vs 61.4
	• Median age (range), years: 64 (34–80) vs 65 (44–85)
	• Cytogenetic risk, n (%)
	  • Standard risk: 46 (92.0) vs 35 (83.3)
	  • High risk: 4 (8.0) vs 7 (16.7)
	Japanese patients (DRd vs Rd group):
	• Male, %: 52.4 vs 60
	• Median age (range), years: 68 (45–80) vs 67

	(50–81)
	• Cytogenetic risk, n (%)
	  • Standard risk: 17 (85.0) vs 10 (66.7)
	  • High risk: 3 (15.0) vs 5 (33.3)

Efficacy in East Asian population	PFS • Median PFS was NR vs. 13.8 months for DRd vs Rd, respectively (HR, 0.42; 95% CI, 0.23–0.76). • The 24-month PFS rate for DRd vs. Rd was 65.6% (95% CI, 50.5–77.0) vs. 32.2% (95% CI, 18.3–46.9). ORR • Overall response rate was 90.2% (n=46/51) patients in the DRd and 72.1% (n=31/43) in Rd. • Stringent complete responses (sCRs): 17 (33.3%) and 5 (11.6%) of patients receiving DRd and Rd, respectively. • CRs: 10 (19.6%) and 4 (9.3%) of patients receiving DRd and Rd. • Very good partial responses (VGPRs): 11 (21.6%) and 8 (18.6%) of patients receiving DRd and Rd. • Partial responses (PRs): 8 (15.7%) vs. 14 (32.6%) of patients receiving DRd and Rd.
Safety in East Asian population	• Higher rates of neutropenia, diarrhea, nasopharyngitis, and pyrexia were observed in the DRd group compared with those in the Rd group, consistent with the overall population. • Serious TEAEs were observed in 26 (51.0%) patients in the DRd group vs. 19 (43.2%) patients in the Rd group, most common being pneumonia.

	IRRs • In daratumumab treated patients, IRR occurred in 25 (49.0%) patients. • Grade 3 IRRs occurred in 6 (11.8%) patients. • Most common IRR was dyspnea, which occurred in 5 (9.8%) patients.
Efficacy in Japanese-only population	PFS • Median PFS was NR vs. 17.6months for DRd vs Rd, respectively (HR, 0.32; 95% CI, 0.11–0.96). ORR • Overall response rate was 90% (n=18/20) patients in the DRd and 60% (n=9/15) in Rd. • Stringent complete responses (sCRs): 9 (45.0%) and 1 (6.7%) of patients receiving DRd and Rd, respectively. • CRs: 1 (5.0%) and 0 (0.0%) of patients receiving DRd and Rd. • Very good partial responses (VGPRs): 5 (25.0%) and 4 (26.7%) of patients receiving DRd and Rd. • Partial responses (PRs): 3 (15.0%) and 4 (26.7%) of patients receiving DRd and Rd.
Safety in Japanese-only population	• Higher rates of neutropenia, diarrhea, nasopharyngitis, and pyrexia were observed in the DRd group compared to Rd group. • Serious TEAEs were observed in 10 (50.0%) patients in the DRd group vs. 4 (26.7%) patients in the Rd group, most common being pneumonia. IRRs • In daratumumab treated patients, IRR occurred in 7 (35.0%) patients. • Grade 3 IRRs occurred in 1 (5.0%) patient.

	• Most common IRR was dyspnea, which occurred in 2 (10.0%) patients.
Conclusion	The addition of daratumumab to Rd led to better PFS as compared with Rd alone in both East Asian patients and Japanese patients from POLLUX, consistent with findings in the global POLLUX population.

Appendix O: One-Way Sensitivity Analysis

- Table O1 Parameter Ranges and Analytical Results (RRMM DVd Model)

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Age	[redacted]		Assuming 10% SE and normal distribution	[redacted]	
Weight			Assuming 10% SE and normal distribution		
Height			Assuming 10% SE and normal distribution		
Discount Rate (Costs)	0%	4%	Per HTA guideline		
Discount Rate (Health)	0%	4%	Per HTA guideline		
Proportion receiving subsequent treatment after	[redacted]		Assuming 10% SE and normal distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
DVd (SC)					
Proportion receiving subsequent treatment after Vd	[redacted]		Assuming 10% SE and normal distribution	[redacted]	
Proportion Hospitalized Dara (SC)			Assuming 10% SE and normal distribution		
Length of Stay Dara (SC)			Assuming 10% SE and normal distribution		
Hospital Fee (Days 1-4)			Assuming 10% SE and Gamma distribution		
Hospital Fee (Days 5-14)			Assuming 10% SE and Gamma distribution		
Hospital Fee (Days 15-21)			Assuming 10% SE and Gamma distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Admin Cost: Dara (SC)	[redacted]		Assuming 10% SE and Gamma distribution	[redacted]	
Admin Cost: Other IV			Assuming 10% SE and Gamma distribution		
Admin Cost: Oral			Assuming 10% SE and Gamma distribution		
% IV for bortezomib			Assuming 10% SE and normal distribution		
Subsequent Tx: Weekly Drug Cost			Assuming 10% SE and Gamma distribution		
Subsequent Tx: Weekly Administration Cost			Assuming 10% SE and Gamma distribution		
Weekly MRU Cost: PFS			Assuming 10% SE and Gamma distribution		
Weekly MRU Cost: PPS			Assuming 10% SE and Gamma distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
End of Life Cost (One-Time)	[redacted]		Assuming 10% SE and Gamma distribution	[redacted]	
Utility: PFS			Assuming 10% SE and lognormal distribution		
Utility: PPS			Assuming 10% SE and lognormal distribution		
Utility Decrement: DVd (SC)			Assuming 10% SE and lognormal distribution		
Utility Decrement: Vd			Assuming 10% SE and lognormal distribution		

- Table O2. Parameter Ranges and Analytical Results (RRMM DRd Model)

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Age	[redacted]		Assuming 10% SE and normal distribution	[redacted]	

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Weight	[redacted]		Assuming 10% SE and normal distribution	[redacted]	
Height			Assuming 10% SE and normal distribution		
Discount Rate (Costs)	0%	4%	Per HTA guideline		
Discount Rate (Health)	0%	4%	Per HTA guideline		
Proportion receiving subsequent treatment after DRd (SC)	[redacted]		Assuming 10% SE and normal distribution		
Proportion receiving subsequent			Assuming 10% SE and normal distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
treatment after Rd					
Proportion Hospitalized Dara (SC)	[redacted]		Assuming 10% SE and normal distribution	[redacted]	
Length of Stay Dara (SC)			Assuming 10% SE and normal distribution		
Hospital Fee (Days 1-4)			Assuming 10% SE and Gamma distribution		
Hospital Fee (Days 5-14)			Assuming 10% SE and Gamma distribution		
Hospital Fee (Days 15-21)			Assuming 10% SE and Gamma distribution		
Admin Cost: Dara (SC)			Assuming 10% SE and Gamma distribution		
Admin Cost: Oral			Assuming 10% SE and Gamma distribution		
Subsequent Tx: Weekly			Assuming 10% SE and Gamma distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Drug Cost					
Subsequent Tx: Weekly Administration Cost	[redacted]		Assuming 10% SE and Gamma distribution	[redacted]	
Weekly MRU Cost: PFS			Assuming 10% SE and Gamma distribution		
Weekly MRU Cost: PPS			Assuming 10% SE and Gamma distribution		
End of Life Cost (One-Time)			Assuming 10% SE and Gamma distribution		
Utility: PFS			Assuming 10% SE and lognormal distribution		
Utility: PPS			Assuming 10% SE and lognormal distribution		
Utility Decrement: DRd (SC)			Assuming 10% SE and lognormal distribution		

Parameter	Parameter Ranges		Rationale	Scope of ICER	
	Lower Limit	Upper Limit		Lower Limit	Upper Limit
Utility Decrement: Rd	[redacted]		Assuming 10% SE and lognormal distribution	[redacted]	