Daratumumab in combination with lenalidomide and dexamethasone improves survival in newly diagnosed transplant-ineligible multiple myeloma:

A parametric network meta-analysis in a United Kingdom setting

Sophie van Beekhuizen[1], Alex Bird[2], Andreas Freitag[3], Zijiao Yuan[1], Timothy Ming[4]
[1]Cytel, Rotterdam, Netherlands; [2]Janssen EMEA, High Wycombe, UK; [3]Cytel, London, UK ; [4]Janssen UK, High Wycombe, UK

KEY TAKEAWAY

- This network meta-analysis confirms previous indirect treatment comparisons which demonstrated that DRd improves survival compared with other treatments for patients with transplant-ineligible newly-diagnosed multiple myeloma.

INTRODUCTION

- Multiple myeloma (MM) is an uncurable condition that is primarily identified by the excessive growth of malignant plasma cells within the bone marrow and the heightened production of M-protein.
- Over the past few years, a range of new treatment regimens have become accessible for MM, significantly enhancing the survival prospects for patients.
- Daratumumab is a first-in-class, fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds to CD38, a cell surface glycoprotein found on the surface of many immune cells, including white blood cells.
- Daratumumab in combination with lenalidomide and dexamethasone (DRd) is indicated for patients with newly-diagnosed transplant-ineligible multiple myeloma (NDMM TIE).
- The phase 3 randomized controlled trial (RCT) MAIA demonstrated that DRd resulted in superior progression-free survival (PFS) and overall survival (OS) compared with lenalidomide and dexamethasone (Rd) in NDMM TIE patients.[1]
- To compare DRd against other relevant treatment combinations in this patient population an indirect treatment comparison can be conducted.
- Previous hazard ratio (HR) network meta-analyses (NMA) have shown DRd to be clinically superior to other treatments.[2] Proportional hazard assumption (PHA) violations in the network, however, require the exploration of advanced NMA methods, as endorsed by NICE in TA917.
- Parametric NMA (PNMA) uses standard parametric models to model long-term survival and is a guideline-recommended method for evidence synthesis for time-to-event outcomes which can be used when the PHA does not hold.[3]

OBJECTIVE

- This research aimed to conduct a PNMA to evaluate OS and PFS for DRd compared with relevant treatments in the United Kingdom (UK) setting.
- Relevant treatment comparators in the UK include Rd, bortezomib with alkylating agent and corticosteroid, and thalidomide with alkylating agent and corticosteroid.

METHODS

Systematic Literature Review

A systematic literature review (SLR) of clinical trials was conducted in June 2017 and updated through December 2021 to identify available treatments for front-line MM.

- Databases searches included Embase, Medline/Medline In-Process, Cochrane CENTRAL and CDSR. Additional conference searches included the American Society of Haematology (ASH), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA), European Society for Medical Oncology (ESMO), (EHA), and International Myeloma Working Group (IMWG).
- Additional meta-analyses/reviews and ClinicalTrials.gov were further searched for potential publications that had not been identified through the database searches.
- Based on the findings of the review the relevant UK comparators include lenalidomide[continuous]-dexamethasone (Rdc), melphalan-prednisone-thalidomide (MPT), bortezomib-melphalan-prednisone (VMP).

PNMA Method

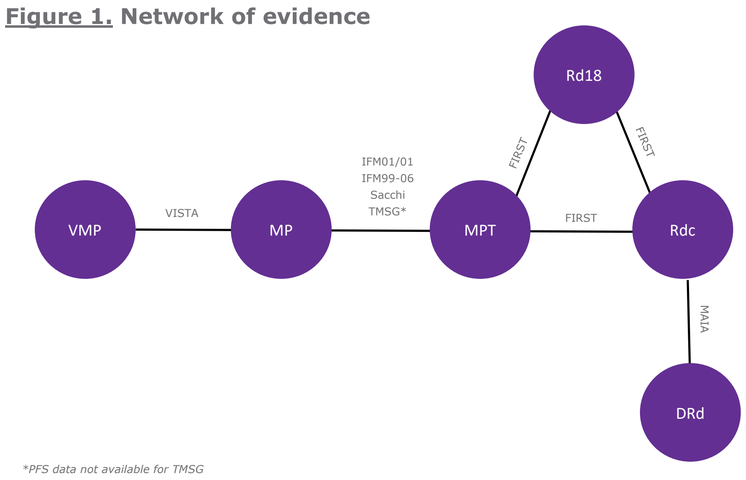
- Pseudo-individual patient-level data were obtained by using the Guyot algorithm to reconstruct data from digitized published Kaplan-Meier curves.[4]
- The PNMA distributions included Weibull, exponential, log-normal, Gompertz, log-logistic and gamma.
- Both OS and PFS PNMAs were performed using the RStan package in R Statistical Software (version 1.2-0).[5]
- The models were run with two chains of 2,000 iterations, and 1,000 were burn-in iterations to generate the posteriors for the defined parameters.
- These analyses were fitted with weakly informative priors.
- The models were compared based on leave-one-out information criteria (LOOIC) and mean survival (95% credible interval [CI]).
- General population mortality correction was not considered in the PNMA analyses.
- MAIA (DRd) was used as the reference trial.

RESULTS

Network of Evidence

- The evidence network consisted of six and seven trials for OS and PFS, respectively (MAIA, FIRST, VISTA, IFM99-06, IFM01/01, Sacchi 2011, TMSG [PFS only]). **(Figure 1)**
- A violation of PHA was observed for FIRST for PFS, and for MAIA and IFM01/01 for OS.

Figure 1. Network of evidence



**PFS data not available for TMSG*

DRd = daratumumab, lenalidomide, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; Rd18 = lenalidomide, dexamethasone 18 cycles; Rdc = lenalidomide, dexamethasone continued; VMP = bortezomib, melphalan, prednisone.

PNMA Model Fit Data

- The LOOIC is an indication of statistical fit in which a lower LOOIC indicates a better fit. The base case model was selected based on the lowest LOOIC.
- **Table 1** shows the LOOIC for each model and indicates that the Gompertz distribution provides the best statistical fit for OS, while the Gamma distribution is the most suitable for PFS.

Table 1. Model fit data — LOOIC

Distribution	OS	PFS
Exponential	21710.94	21553.5
Weibull	21679.72	21460.8
Gompertz	21661.93	21495.8
Loglogistic	21771.26	21541.4
Lognormal	21900.14	21698.5
Gamma	21684.03	21458.6

OS = overall survival; PFS = progression-free survival

PNMA Results

- DRd showed the best survival irrespective of model choice in both OS and PFS **(Table 2)**.
  - **OS:** DRd resulted in the longest mean OS at 11.6 years (95% CI: 7.2, 36.1), followed by Rdc (5.7 [4.9, 7.0]), MPT (4.9 [4.0, 6.3]), and VMP (4.4 [3.3, 6.3]).
  - **PFS:** DRd demonstrated the longest mean PFS (8.0 years [6.7, 9.8]), followed by Rdc (4.0 [3.5, 4.7]), VMP (2.7 [1.8, 4.0]), and MPT (2.6 [2.1, 3.2]).
- **Figure 2** displays the PNMA predictions for short-term and long-term survival using MAIA as the reference trial for both OS and PFS.

Table 2. Mean survival, years (95% credible interval)

	Exponential	Weibull	Gompertz	Loglogistic	Lognormal	Gamma
OS						
DRd	11.7 (10.1-13.8)	13.1 (10-18.1)	11.6 (7.2-36.1)	21.3 (16.8-26.7)	27.3 (21.9-33.4)	12.9 (10.2-16.7)
Rdc	8.1 (7.0-9.4)	6.8 (5.8-8.2)	5.7 (4.9-7.0)	11.3 (9.2-14.2)	13.2 (10.4-16.9)	7.2 (6.1-8.6)
Rd18	8.4 (6.7-10.4)	7.0 (5.5-9.2)	6.2 (4.9-12.4)	11.1 (8.1-15.2)	11.8 (8.2-16.6)	7.2 (5.7-9.3)
MPT	6.5 (5.2-7.9)	5.6 (4.4-7.3)	4.9 (4.0-6.3)	9.2 (6.6-12.7)	9.8 (6.7-13.9)	5.8 (4.6-7.4)
MP	4.3 (3.2-5.6)	3.9 (2.8-5.5)	3.6 (2.8-5.0)	6.3 (3.8-10.2)	5.6 (3.3-9.5)	3.9 (2.9-5.4)
VMP	6.0 (4.2-8.5)	5.4 (3.6-8.6)	4.4 (3.3-6.3)	10.1 (5.7-16.6)	10.9 (5.8-18.3)	5.7 (3.8-8.5)
PFS						
DRd	7.5 (6.5-8.7)	8.3 (6.6-10.8)	11.2 (5.8-27.5)	14.6 (11.9-18.3)	16.9 (13.5-20.8)	8 (6.7-9.8)
Rdc	4.1 (3.6-4.7)	4 (3.5-4.8)	4 (3.3-8.1)	6.7 (5.5-8.4)	8.1 (6.4-10.3)	4 (3.5-4.7)
Rd18	2.7 (2.3-3.3)	2.6 (2.1-3.2)	2.5 (2.1-2.9)	3.4 (2.5-4.6)	3.7 (2.7-5.3)	2.5 (2.1-3.1)
MPT	2.7 (2.3-3.3)	2.5 (2.1-3.2)	2.5 (2.1-2.9)	3.8 (2.8-5.3)	4.2 (2.9-6)	2.6 (2.1-3.2)
MP	1.6 (1.3-2.2)	1.6 (1.2-2.2)	1.6 (1.3-2.1)	2.4 (1.6-3.8)	2.4 (1.6-3.9)	1.6 (1.2-2.1)
VMP	2.8 (2-4.1)	2.7 (1.8-4.1)	2.4 (1.6-23.9)	4.5 (2.5-8.1)	5.8 (3-11.4)	2.7 (1.8-4)

DRd = daratumumab, lenalidomide, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; OS = overall survival; PFS = progression-free survival, Rd18 = lenalidomide, dexamethasone 18 cycles; Rdc = lenalidomide, dexamethasone continued; VMP = bortezomib, melphalan, prednisone.

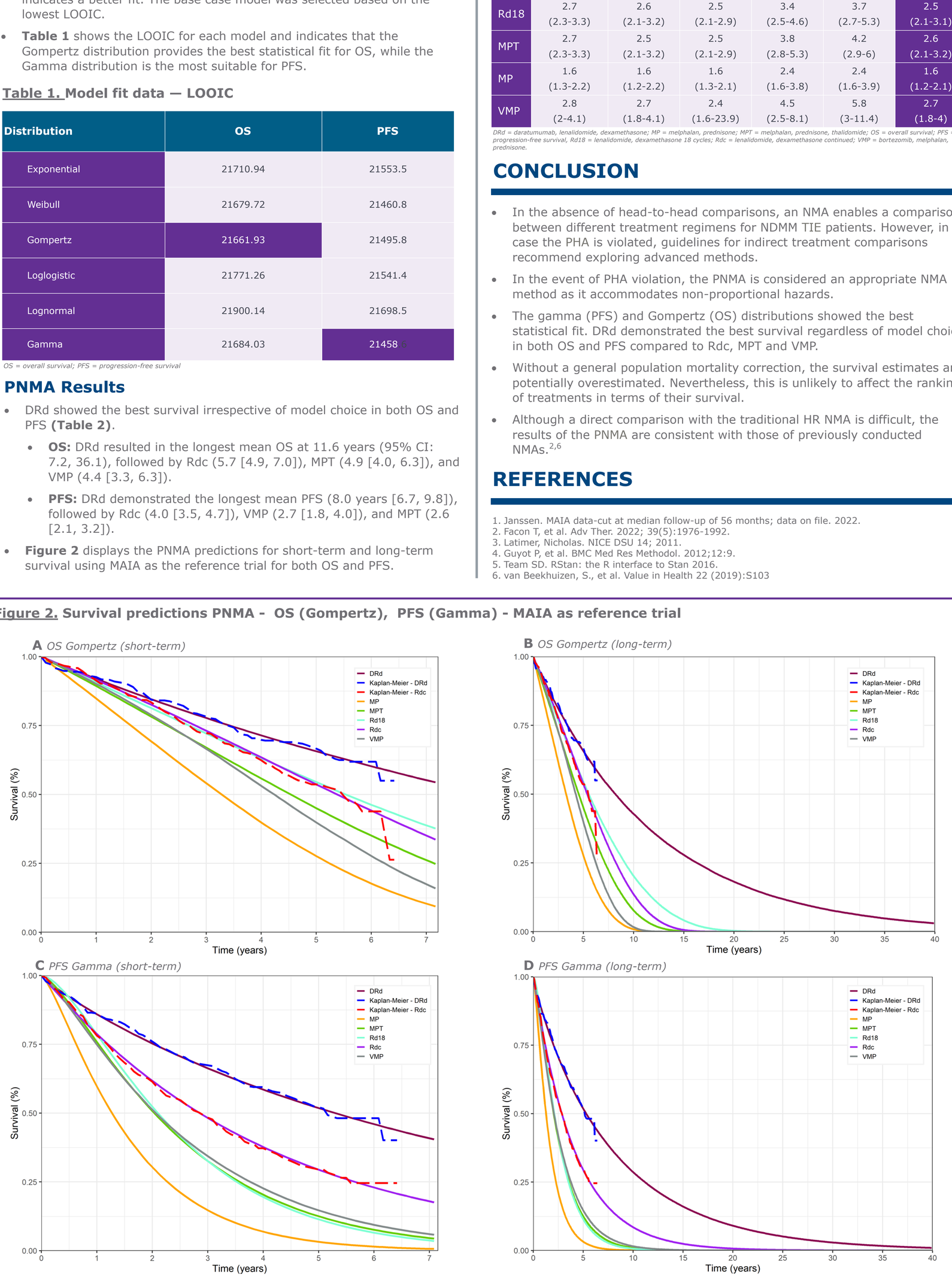
CONCLUSION

- In the absence of head-to-head comparisons, an NMA enables a comparison between different treatment regimens for NDMM TIE patients. However, in case the PHA is violated, guidelines for indirect treatment comparisons recommend exploring advanced methods.
- In the event of PHA violation, the PNMA is considered an appropriate NMA method as it accommodates non-proportional hazards.
- The gamma (PFS) and Gompertz (OS) distributions showed the best statistical fit. DRd demonstrated the best survival regardless of model choice in both OS and PFS compared to Rdc, MPT and VMP.
- Without a general population mortality correction, the survival estimates are potentially overestimated. Nevertheless, this is unlikely to affect the ranking of treatments in terms of their survival.
- Although a direct comparison with the traditional HR NMA is difficult, the results of the PNMA are consistent with those of previously conducted NMAs.[2,6]

REFERENCES

1. Janssen. MAIA data-cut at median follow-up of 56 months; data on file. 2022.
2. Facon T, et al. Adv Ther. 2022; 39(5):1976-1992.
3. Latimer, Nicholas. NICE DSU 14; 2011.
4. Guyot P, et al. BMC Med Res Methodol. 2012;12:9.
5. Team SD. RStan: the R interface to Stan 2016.
6. van Beekhuizen, S., et al. Value in Health 22 (2019):S103

Figure 2. Survival predictions PNMA - OS (Gompertz), PFS (Gamma) - MAIA as reference trial



DRd = daratumumab, lenalidomide, dexamethasone; MP = melphalan, prednisone; MPT = melphalan, prednisone, thalidomide; OS = overall survival; PFS = progression-free survival, Rd 18 = lenalidomide, dexamethasone 18 cycles; Rdc = lenalidomide, dexamethasone continued; VMP = bortezomib, melphalan, prednisone.