The Relationship Between Progression-Free Survival and Overall Survival in Relapsed/Refractory Multiple Myeloma: A Meta-Regression of Clinical Trial Data

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Treatment effect on PFS is positively associated with treatment effect on OS in patients with RRMM in the 2L+ setting

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Background

- Improved survival outcomes with novel therapies in patients with RRMM have resulted in increased time to obtain mature OS data[1,2]
- To provide important clinical insights without prolonged follow-up periods, there is a need for surrogate endpoints that support estimation of OS

Aim

- To investigate the association between treatment effect on PFS and treatment effect on OS based on published trials in 2L+ RRMM

Methods

- A systematic literature review was conducted (2008 to February 2024) to identify efficacy and safety data from phase 2/3 RRMM clinical trials
- Studies were included if they had ≥50 patients per arm and reported relevant outcomes for patients aged ≥18 years in the 2L+ RRMM setting per the Population, Intervention, Comparison, Outcomes, Study design (PICOS) criteria. A feasibility assessment was performed to evaluate the heterogeneity between studies and determine if the endpoint surrogacy study was feasible
- Studies were excluded if they did not report outcome data required for the analysis
- Trial-level surrogacy was explored using HR of PFS and OS. Arm-level surrogacy was explored using median values for PFS and OS
- Spearman's correlation coefficient estimated strength of associations and weighted least squares (WLS) regression analyses quantified relationships between PFS and OS HRs and absolute medians
- Based on the fitted WLS model, the surrogate threshold effect (STE) was estimated to determine the relative treatment effect on PFS required to forecast a significant treatment effect on OS. Sensitivity analyses (for studies that assessed cross-over, phase 3 studies with immature OS, and studies of non-licensed treatments) were also performed to address heterogeneity and potential biases
- Finally, based on the observed PFS, the WLS models were used to predict the OS HR for belantamab mafodotin with pomalidomide/dexamethasone (BPd) in the phase 3 DREAMM-8 trial in patients with RRMM[3]

Results

Table 1: **Thirty studies were included in the base-case analysis, 26 of which were phase 3, 5 allowed cross-over from comparator to treatment arm, and most included patients in the 2L+ or 2–4L setting**

Study	Phase	Cross-over	Treatment lines	Total sample size
ADMYRE[4]	3	Yes	3–6L	255
APOLLO[5]	3	Yes	2L+	304
ARROW[6]	3	No	3–4L	478
ASPIRE[7]	3	No	2–4L	792
BELLINI[8]	3	No	2–4L	291
BOSTON[9]	3	No	2–4L	402
CANDOR[10]	3	No	2–4L	466
CARTITUDE-4[11]	3	No	2–4L	419
CASTOR[12]	3	No	2L+	498
CHICTR-IPR[13]	3	No	3L+	417
COLUMBA[14]	3	No	4L+	522
ELOQUENT-2[15]	3	No	2–4L	646
EudraCT 2013-003265-34[16]	2	No	2L	111
FOCUS[17]	3	No	4L+	315
GEM_KyCyDex[18]	2	No	2–4L	197
ICARIA-MM[19]	3	No	3L+	307
IKEMA[20]	3	No	2–4L	302
KEYNOTE-183[21]	3	No	3L+	249
LEPUS[22]	3	Yes	2L+	211
NCT00602511[23]	3	Yes	2L+	131
NCT00401843[24]	2	No	2–4L	286
NCT01084252[25]	2	Yes	4L+	165
NIMBUS; MM-003[26]	3	No	3L+	455
OCEAN[27]	3	No	3–5L	495
OPTIMISMM[28]	3	No	2–4L	559
OPTIMUM[29]	3	No	2–4L	499
PANORAMA-1[30]	3	No	2–4L	768
POLLUX[31]	3	No	2L+	569
TOURMALINE[32]	3	No	2–4L	722
VANTAGE 088[33]	3	No	2–4L	637

Figure 1: **(A) Significant positive correlation was found between PFS and OS HRs (Spearman's coefficient 0.52 [95% CI: 0.13–0.83]), and the WLS model indicated moderate* predictive power for HRs (slope 0.53; p<0.001; R^2=0.42). (B) STE forecast a PFS HR of 0.749 or lower would result in a significant OS treatment effect**

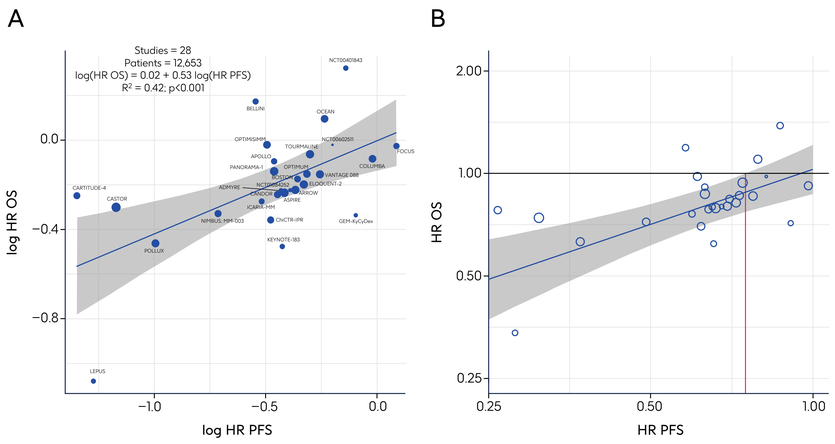
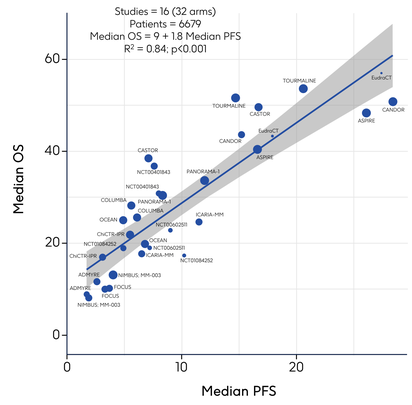


Figure 2: **Absolute medians of PFS and OS were significantly positively correlated (Spearman's coefficient 0.88 [95% CI: 0.72–0.94]), and the WLS model indicated moderate predictive power for absolute medians (slope 1.8; p<0.001; R^2=0.84)**



*Limited guidelines are available for surrogate endpoint acceptance cutoffs[34]

- Based on the reported median PFS of 32.6 months (95% CI: 21.1–not reached) for BPd and the PFS HR of 0.52 (95% CI: 0.37–0.73) in DREAMM-8,[3] WLS models forecasted that BPd would have a median OS of 67.8 months (95% PI: 47.1–not reached) and an OS HR of 0.73 (95% PI: 0.61–0.87) in DREAMM-8
  - Follow-up is ongoing for OS in DREAMM-8, but the study showed a trend favoring BPd[3]
- Sensitivity analyses, including those that excluded studies that allowed cross-over, phase 3 studies with immature OS, and studies of non-licensed treatments, were consistent with the base models

Conclusions

Treatment effect on PFS was positively associated with treatment effect on OS in 2L+ RRMM trials, indicating that substantial PFS benefits are expected to lead to OS benefits once data maturity is reached

- These data will aid in clinical trial design when considering primary endpoints for studies in this setting

Based on the PFS HR observed in the DREAMM-8 trial, the WLS model forecasted an OS HR favoring BPd over PVd

Abbreviations

2L+, second-line or later; BPd, belantamab mafodotin, pomalidomide, and dexamethasone; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PI, prediction interval; PVd, pomalidomide, bortezomib and dexamethasone; RRMM, relapsed/refractory multiple myeloma; STE, surrogate threshold effects; WLS, weighted least squares

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SP, **SK**, and **CW** are employees of OPEN Health HEOR & Market Access, and **SP** has a spouse employed by the Belgian government. **MP**, **BZ**, and **SM** are employees of GSK and hold financial equities in GSK.

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