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*Original Article*

# Efficacy and safety of pegylated liposomal doxorubicin for multiple myeloma: a systematic review and meta-analysis of randomized controlled trials

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**Abstract:** Pegylated liposomal doxorubicin (PLD) which is an improved formulation of doxorubicin has been used for the treatment of multiple myeloma (MM). We perform a systemic review to evaluate the efficacy and safety of PLD in patients with MM. Three Randomized controlled trials (RCTs) involving 1100 patients were included. One RCT evaluated PLD versus no PLD for patients with relapsed or refractory myeloma. Results showed that PLD prolonged time to progression (TTP) (HR 0.55, 95% CI 0.43 to 0.71; moderate quality of evidence) and progression free survival (PFS) (HR 0.59, 95% CI 0.46 to 0.76; moderate quality of evidence), but did not confer significant benefit on overall survival (OS). Patients are more likely to experience grade 3/4 myelosuppression. The other two RCTs assessed PLD versus conventional doxorubicin for newly diagnosed MM. Results showed that no difference was found in OS, TTP, PFS, response rates, although PLD reduced the risks of grade 3/4 neutropenia. In summary, compared with no PLD for patients with relapsed or refractory myeloma, PLD prolonged TTP and PFS, but did not confer significant benefit on OS. The currently available evidence did not show fewer AEs between PLD and conventional doxorubicin used in induction therapy of newly diagnosed myeloma.

**Keywords:** Pegylated liposomal doxorubicin, multiple myeloma, systematic review, meta-analysis

## Introduction

Multiple myeloma (MM) is a malignant neoplasm of plasma cells and accounts for approximately 10% of all hematologic malignancies [1]. Although introduction of the so-called novel agents, proteasome inhibitors and immunomodulatory drugs, and improved supportive care have resulted in significantly better outcome, the disease remains incurable and relapse is inevitable [2]. Therefore, appropriate treatment strategies for MM are urgently needed.

The anthracycline doxorubicin has long been considered one of the most active agents for the treatment of MM [3, 4]. However, treatment with doxorubicin may be complicated by acute and chronic side effects. The acute side effects of doxorubicin, such as myelosuppression, nausea, vomiting, and arrhythmias, are usually clinically manageable and reversible. However, the chronic side effects of the drug, such as cardiomyopathy and, ultimately, congestive heart failure, are always irreversible and have a negative effect on prognosis [5, 6].

Pegylated liposomal doxorubicin (PLD) was developed with the aim of overcoming the shortcomings of traditional doxorubicin while maintaining its efficacy. PLD is a form of the hydrochloride salt of the anthracycline antineoplastic antibiotic doxorubicin encapsulated in liposomes with surface-bound methoxypolyethylene glycol. It is commonly used in combination therapies for MM as a replacement for traditional doxorubicin, and has demonstrated several advantages over the original drug: PLD has a longer half-life than the traditional agent, and is able to extravasate through abnormal bone marrow vessels, exposing malignant plasma cells to higher concentrations for longer times. Pegylated liposomal doxorubicin also modulates the toxicity of traditional doxorubi-

cin, in particular, the cardiac adverse effects [7].

Recently, several studies reported that PLD has promising clinical benefit and may be an effective treatment option for patients with MM [8-10]. However, large multicenter randomized controlled trials are few, and conclusive evidence is unavailable. Therefore, we conducted this systematic review and meta-analysis of clinical trials investigating the efficacy and safety of PLD in patients with MM.

## Methods

### *Data sources and searches strategy*

The following electronic databases were searched: MEDLINE/Ovid (from 1946 to August Week 4 2016), Embase/Ovid (from 1974 to September 2016), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2016, Issue 9), Chinese BioMedical Literature Database (1978 to September 2016). For the first search, we used terms including the medical subject headings "multiple myeloma" or "plasmacytoma", text words "myeloma" "myelom*", "Plasmacytoma", "Plasmacytom*", "Plasmocytoma" or "Plasmocytom*". For the second search, terms included "Doxorubicin", "pegylated liposomal doxorubicin", "Doxil", "Evacet", "caelyx", "myocet"or "rubex". The results from both searches were combined using Boolean Operator "AND". A filter for identifying the randomized controlled trials recommended by The Cochrane Collaboration [11] was used to filter out non-randomized studies in MEDLINE and Embase. The conference proceedings were identified by searching the Conference Proceedings Citation Index-Science (CPCI-S). Ongoing trials were identified through searching the databases of clinical trial registries (http://clinicaltrials.gov and http://www.controlled-trials.com) in September 2016. Reference lists of all included studies and of reviews related to the topic of the present systematic review were manually searched for other potentially eligible studies. No language and publication status restrictions were applied.

### *Study selection and data collection*

We selected randomized controlled trials (RCTs). The participants were patients with multiple myeloma of any stage. The intervention was PLD at any dose, for any duration, as monotherapy or in combination with other agent(s). Acceptable comparisons were PLD vs. placebo, PLD vs. no PLD, or PLD vs. other active agent(s). We excluded RCTs involving patients with MM and other malignancies unless subgroup data are available for the patients with MM. Potential eligible studies were selected from the search results according to titles and abstracts and the eligibility of these studies for inclusion was further confirmed after full text papers were reviewed, independently by two review authors (JL and JZ). Disagreements were resolved by the third author (JC or ZZ).

Data extraction was performed independently by two reviewers (ZZ and DQ). Disagreements were resolved by discussion until consensus was obtained. Updated results were sought from the trials authors as possible as we could, particularly for those published only as meeting abstracts. The data extracted from the trials were entered into the Review Manager (RevMan) software version 5.3 (the Cochrane Collaboration).

### *Outcome measures*

The primary outcome was overall survival (OS), which was defined as time interval from random allocation to death. Alternative definitions, such as time interval from the start of treatment to death were also included and noted as a potential source of heterogeneity. The secondary outcomes were disease control, such as time to progression (TTP) and progression free survival (PFS), complete responses (CR), very good partial responses (VGPR), overall responses (ORR-partial and complete responses), and adverse events (AEs). TTP was defined as time from randomization to progression. PFS was defined as time from randomization to progression or death. Response with any definition was included.

### *Assessment of risk of bias in included studies*

Two independent authors (ZZ and JL) assessed methodological quality of the included studies. As recommended in the Cochrane Handbook for Systematic Review of Interventions [11], assessment tool included six specific domains, namely sequence generation, allocation concealment, blinding (patients, personnel, and

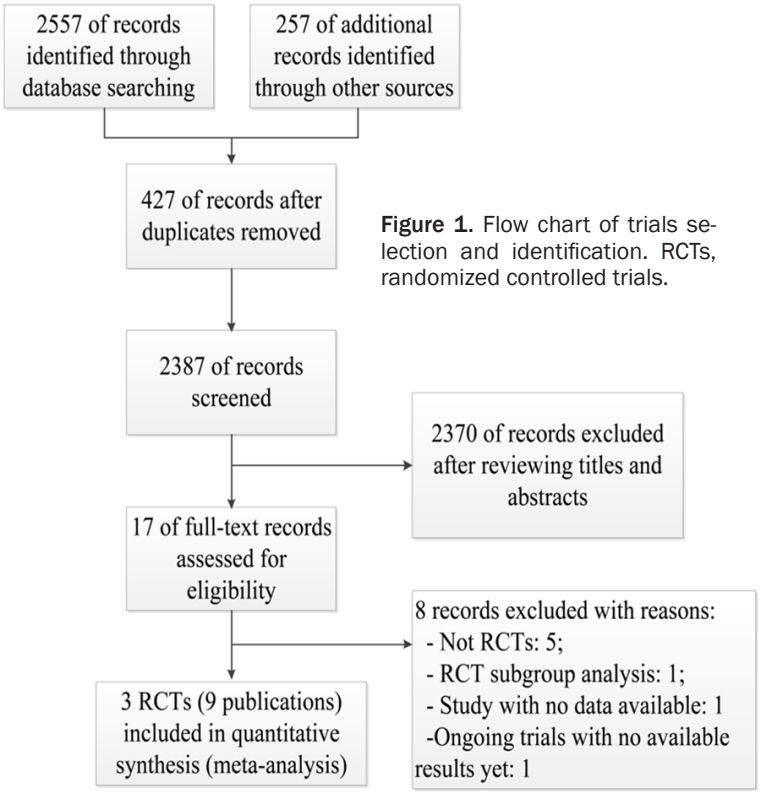


**Figure 1.** Flow chart of trials selection and identification. RCTs, randomized controlled trials.

outcome assessors), incomplete outcome data, selective outcome reporting and other potential bias. The risk of bias was judged against the following questions: 1) Was the allocation sequence adequately generated? 2) Was the treatment allocation adequately concealed? 3) Was knowledge of the allocated interventions adequately prevented during the study? 4) Were incomplete outcome data adequately addressed? 5) Were reports of the study free of suggestion of selective outcome reporting? 6) Was the study apparently free of other problems that could put it at a risk of bias? In all cases, we evaluated each criterion on a three-point scale: low risk of bias, high risk of bias, or unclear [11]. We resolved disagreements by discussion with a third reviewer (JC) until we obtained consensus.

*Data synthesis and statistical analysis*

We used RevMan 5.3 software for all meta-analyses. First we calculated hazard ratio (HR) and its variance for time-to-event data (OS and TTP/PFS) whenever the studies did not report, using previously reported methods [12-14]. Then, log (HRs) and their variances of all included trials were pooled together, using inverse variance random-effects model. The results were presented as a HR and 95% confidence interval (CI). Relative risks (RRs) and 95% CI for dichotomous data (response rate and AEs) were calculated using Mantel-Haenszel method. We performed grading of the evidence using the software GRAD Epro 3.6 (GRADE pro 2011), which was developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org).

Heterogeneity was analyzed by the chi-squared test with significance set at $P$ value 0.10, and the quantity of heterogeneity was measured by $I^2$ statistic [15]. The origins of heterogeneity, if present, were explored according to differences in methodological quality and characteristics of participants and intervention. Subgroup analyses were conducted on patients patient' characteristics, e.g.: age (e.g. adults aged less than 65 years or 65 and older); special cytogenetic features (e.g. del(13) or t(11;14)); or disease status (untreated or refractory/relapsed). Sensitivity analyses were performed on methodological quality and publication status. Publication bias was assessed unless too few studies were included.

## Results

*Description of studies*

*Results of the search*

We identified 2814 potentially relevant references through database searches and hand searching. 427 records were excluded after deduplication. By screening titles and abstracts, we identified 17 publications as potentially eligible for this review. After evaluating full texts of these publications, we excluded eight records and included three trials [10, 16, 17] (nine publications [10, 16-23]). The overall number of references screened, identified, selected, excluded and included is documented according to the PRISMA flow diagram (**Figure 1**).

**Table 1.** Characteristics of included studies

| Studies | Participants (Number) | Interventions | | Outcomes | Publication status |
|---|---|---|---|---|---|
| | | Expt | Ctrl | | |
| Orlowski 2016 [10] | Relapsed or refractory myeloma (646) | PLD plus bortezomib: PLD 30 mg/m$^2$ intravenous infusion on day 4 of each cycle after bortezomib. | Bortezomib alone: bortezomib 1.3 mg/m$^2$ intravenous bolus on days 1, 4, 8, and 11 of every 21 days cycle. | OS; TTP; PFS; ORR; CR; VGPR; PR; AEs | Full-text |
| Dimopoulos 2003 [16] | Previously untreated myeloma (259) | VAD doxil regimen: vincristine 2 mg on day 1, liposomal doxorubicin (doxil) 40 mg/m$^2$ on day 1 and dexamethasone 40 mg daily for 4 days (every 28 days for four courses). In courses 1 and 3, in both arms, dexamethasone was also given on days 9-12 and 17-20. | VAD bolus regimen: vincristine 0.4 mg and doxorubicin 9 mg/m$^2$ and dexamethasone 40 mg daily for 4 consecutive days. | OS; TTP; CR; PR; AEs | Full-text |
| Rifkin 2006 [17] | Previously untreated myeloma (192) | DVd regimen: PLD 40 mg/m$^2$ IV over 1 hour plus vincristine 1.4 mg/m$^2$ to a maximum of 2.0 mg IV over 5 minutes on Day 1 and dexamethasone 40 mg per day orally on Days 1-4 of each 28. | VAd regimen: vincristine 0.4 mg per day and conventional doxorubicin 9 mg/m$^2$ per day intravenously (IV) over 96 hours and dexamethasone 40 mg per day orally on Days 1-4 of each 28-day cycle. | OS; PFS; ORR; CR; AEs | Full-text |

Abbreviation: Expt, experimental arm; Ctrl, control arm; BOZ, Bortezomib; PLD, pegylated liposomal doxorubicin; OS, overall survival; TTP, time to disease progression; PFS, progression free survival; CR, complete response; PR, partial response; AEs, adverse events.

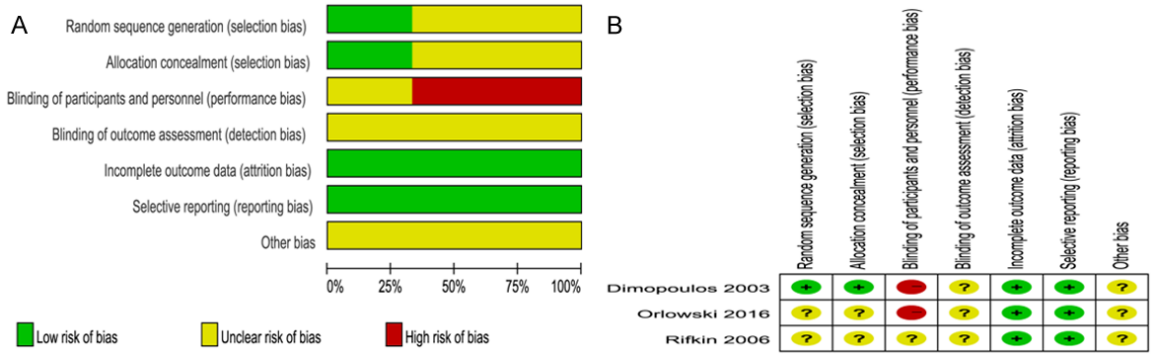


**Figure 2.** Risk of bias for the included studies. A: Overall 'Risk of bias' assessment; B: Summary of the risk of bias for each included trial.

*Included studies*

Three studies [10, 16, 17] with 9 publications [10, 16-23] with 1100 patients were included in the systematic review. All these three trials were conducted between 1999 and 2006 and published as full-text. The characteristics of the included studies were summarised in the **Table 1**. Among these trials, one trial involving 646 patients evaluated PLD versus no PLD [10], and the other two trials involving 454 patients compared PLD with conventional doxorubicin [16, 17].

*Design:* All included studies were two-armed RCTs. One study [10] randomised relapsed or refractory patients to receive PLD plus bortezomib or the same bortezomib regimen alone. Two studies [16, 17] randomised newly diagnosed patients to receive pegylated liposomal doxorubicin + vincristine + dexamethasone induction or doxorubicin + vincristine + dexamethasone induction.

*Sample sizes:* The sample sizes of the included trials were 192 [17], 259 [16] and 646 [10], respectively.

*Location:* All these trials were multi-centre trials conducted either within a single country or in several countries. Two trials in newly diagnosed patients was conducted in Greece [16] and US [17], respectively. One trial in relapsed or refractory patients was conducted in 109 locations [10].

*Participants:* All these trials included both male and female patients with a diagnosis of multi-

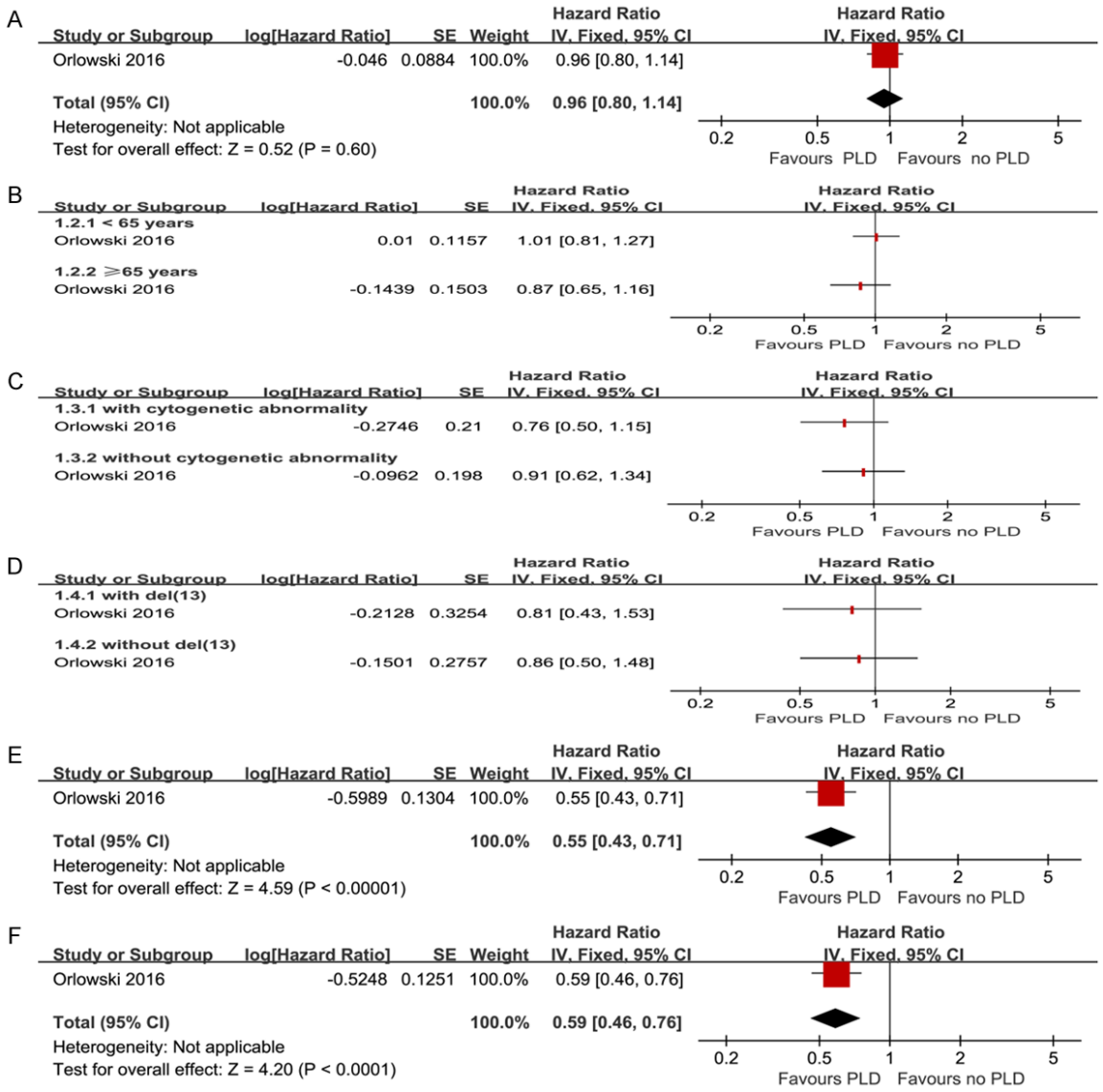


**Figure 3.** Meta-analysis of overall survival (OS) and disease control in the trials comparing PLD with no PLD. A: OS; B: OS subgroup analysis by age; C: OS subgroup analysis by cytogenetic abnormality; D: OS subgroup analysis by del(13); E: Time to progression; F: Progression free survival. SE, standard error; IV, inverse variance; CI, confidence interval.

ple myeloma who were at least 18 years of age. Two studies included only patients with newly diagnosed multiple myeloma [16, 17]. One study included only patients with relapsed or refractory multiple myeloma [10].

*Intervention:* Two studies assessed the role of PLD versus conventional doxorubicin in induction therapy of patients with newly diagnosed multiple myeloma [16, 17]. The dose of PLD was 40 mg/m$^2$ in each course. Orlowski study [10] compared PLD plus bortezomib with bortezomib alone treating patients with relapsed disease who had received one or more lines of therapy, or have been refractory to initial treatment. The dose of PLD was 30 mg/m$^2$ in each cycle.

*Outcomes:* OS data were available from all three studies [10, 16, 17]. TTP was reported in two studies [10, 16]. PFS was reported in two studies [10, 17]. ORR and CR were reported in all trials, but VGPR only in the Orlowski study [10]. AEs were also reported in all trials [10, 16, 17], although the level of AE reporting varied. We extracted and analyzed grade 3 and grade

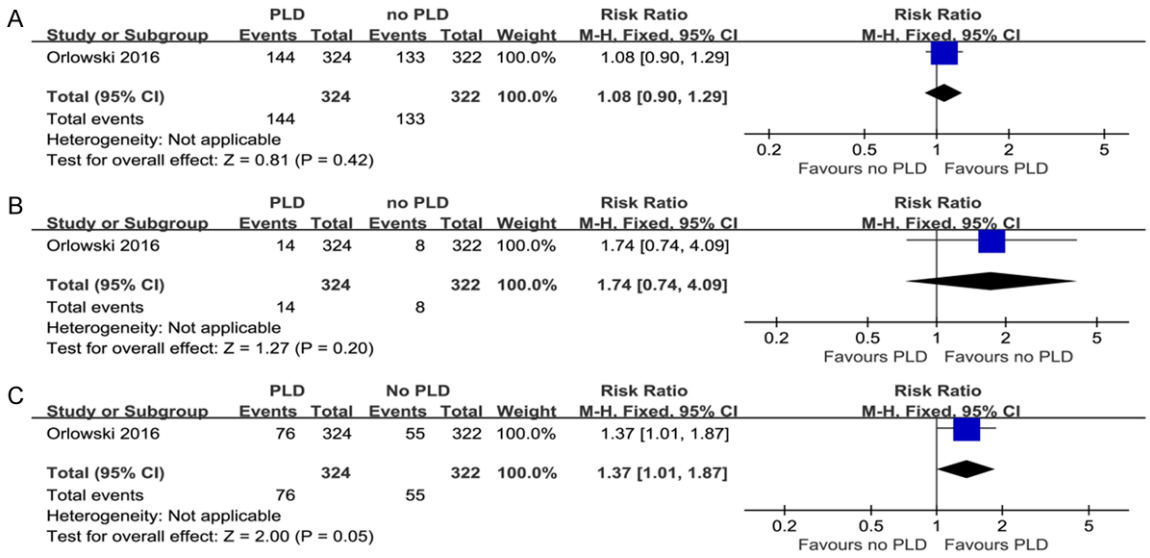


**Figure 4.** Meta-analysis of response rates in the trials comparing PLD with no PLD. A: Complete responses; B: Overall responses; C: Very good partial response. M-H, Mantel-Haenszel; CI, confidence interval.

4 AEs. None of the studies provided data regarding quality of life (QoL).

*Excluded studies*

Eight records were excluded after detailed evaluation of full-text publications for the following reasons: non-randomised studies [24-28]; RCT subgroup analysis [29]; study with no data available [30], ongoing study that fulfilled our pre-defined inclusion criteria but had no available result yet [31].

*Risk of bias in included studies*

Results of the overall 'Risk of bias' assessment was presented in **Figure 2A** and a summary of the risk of bias for each included trial was presented in **Figure 2B**.

*Allocation (selection bias):* All included studies stated that they were 'randomised'. One study stated that random sequence was generated by referring to random permuted blocks [16]. We judged the study as low risk of bias for random sequence generation. The remaining two studies [10, 17] did not report the method of random sequence generation. We judged these studies as unclear risk of bias for the domain. Allocation was adequately concealed in one study (central allocation) [16]. It was judged as low risk of bias for allocation concealment. No information was available for the other studies [10, 17] and they were judged as unclear risk of bias for the domain.

*Blinding (performance bias and detection bias):* One trial [10] allocation was open-label, with both participants and trial personnel aware of the treatments administered. Open-label study is more susceptible to performance bias, therefore we judged the potential risk of bias for blinding of participants and personnel to be high. In another trial [16], patients were not blinded so we judged the potential risk of bias for blinding of participants and personnel to be high. One trial [17], it did not reported information for blinding of participants and trial personnel. We considered the risk of bias for blinding of participants and personnel as unclear. None of the included studies provided information for blinding of the outcome assessors. We considered the risk of detection bias as unclear.

*Incomplete outcome data (attrition bias):* All included studies [10, 16, 17] explicitly provided the number of and reasons for withdrawal or loss to follow-up. We judged the three studies as low risk of attrition bias.

*Selective reporting (reporting bias):* In all the included studies, the protocol is available, and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way. We judged the risk of reporting bias as low.

*Other potential sources of bias:* No other potential sources of bias were identified for the three included RCTs. They were left as unclear risk of bias for this domain.

**Table 2.** Summary of findings for comparison of PLD and no PLD for multiple myeloma

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | No PLD | PLD | | | |
| OS | 798 per 1000 | 785 per 1000 (722 to 839) | HR 0.96 (0.8 to 1.14) | 646 (1 study) | ⊕⊕⊕⊕ high |
| TTP | 870 per 1000 | 674 per 1000 (583 to 765) | HR 0.55 (0.43 to 0.71) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| PFS | 832 per 1000 | 651 per 1000 (560 to 743) | HR 0.59 (0.46 to 0.76) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| Overall response | 413 per 1000 | 446 per 1000 (372 to 533) | RR 1.08 (0.9 to 1.29) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| CR | 25 per 1000 | 43 per 1000 (18 to 102) | RR 1.74 (0.74 to 4.09) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| VGPR | 171 per 1000 | 234 per 1000 (173 to 319) | RR 1.37 (1.01 to 1.87) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| AEs-Neutropenia (Grade 3/4) | 143 per 1000 | 290 per 1000 (211 to 399) | RR 2.03 (1.48 to 2.79) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| AEs-Febrile neutropenia (Grade 3/4) | 6 per 1000 | 9 per 1000 (2 to 55) | RR 1.49 (0.25 to 8.86) | 646 (1 study) | ⊕⊕ΘΘ low[1,2] |
| AEs-Thrombocytopenia (Grade 3/4) | 152 per 1000 | 219 per 1000 (158 to 304) | RR 1.44 (1.04 to 2) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| AEs-Anemia (Grade 3/4) | 87 per 1000 | 90 per 1000 (55 to 147) | RR 1.03 (0.63 to 1.69) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| AEs-Cardiac events (Grade 3/4) | 9 per 1000 | 6 per 1000 (1 to 37) | RR 0.66 (0.11 to 3.94) | 646 (1 study) | ⊕⊕ΘΘ low[1,2] |
| AEs-Neuropathy (Grade 3/4 ) | 28 per 1000 | 12 per 1000 (4 to 40) | RR 0.44 (0.14 to 1.42) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |
| AEs-Nausea (Grade 3/4) | 3 per 1000 | 22 per 1000 (3 to 175) | RR 6.96 (0.86 to 56.22) | 646 (1 study) | ⊕⊕ΘΘ low[1,2] |
| AEs-Hand-foot syndrome | 0 per 1000 | 0 per 1000 (0 to 0) | RR 100.38 (6.22 to 1620) | 646 (1 study) | ⊕ΘΘΘ very low[1,3] |
| AEs-Alopecia | 3 per 1000 | 6 per 1000 (1 to 68) | RR 1.99 (0.18 to 21.81) | 646 (1 study) | ⊕⊕ΘΘ low[1,2] |
| AEs-Treatment-related deaths | 121 per 1000 | 86 per 1000 (55 to 137) | RR 0.71 (0.45 to 1.13) | 646 (1 study) | ⊕⊕⊕Θ moderate[1] |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; OS, overall survival; TTP, time to disease progression; PFS, progression free survival; CR, complete response; PR, partial response; AEs, adverse events. [1]Downgraded one level due to lack of blinding (subjective outcomes are highly susceptible to biased assessment). [2]Downgraded one level due to low number of events, wide CI. [3]Downgraded two levels due to very low number of events, very wide CI.

## Effects of interventions

*Comparison 1: PLD versus no PLD*

One trial compared PLD with no PLD in relapsed or refractory MM [10]. OS, TTP, PFS, and response rate were reported in the trial, but not quality of life.

*Primary outcomes*

*Overall survival (OS):* There was no significant difference in OS between PLD versus no PLD group (HR 0.96, 95% CI 0.80 to 1.14; **Figure 3A**). Subgroup analysis of OS by age (< 65 years or ≥65 years) showed no OS benefit of PLD in both age groups (**Figure 3B**). HRs were 1.01 (95% CI 0.81 to 1.27 and 0.87 (95% CI 0.65 to 1.16), respectively. Neither subgroup analysis for cytogenetic abnormality (**Figure 3C**) found benefit of PLD. HRs were 0.76 (95% CI 0.50 to 1.15) and 0.91 (95% CI 0.62 to 1.34) , respectively. In the subgroup analysis of OS by del(13), we did not find sufficient evidence that OS versus no PLD for relapsed or refractory multiple myeloma was different between the subgroups (**Figure 3D**). In patients with del(13) and without del(13), the HR was 0.81 (95% CI 0.43 to 1.53) and 0.86 (95% CI 0.50 to 1.48), respectively.

*Secondary outcome measures*

Time to progression (TTP) and Progression free survival (PFS).

The PLD regimen resulted in a significantly longer TTP (HR 0.55, 95% CI 0.43 to 0.71; **Figure 3E**) and better PFS (HR 0.59, 95% CI 0.46 to 0.76; **Figure 3F**) than no PLD regimen.

*Response rate:* Orlowski study [10] reported ORR, CR and VGPR. There were no statistically significant differences between arms in ORR (RR 1.08, 95% CI 0.90 to 1.29; **Figure 4A**) and CR (RR 1.74, 95% CI 0.74 to 4.09; **Figure 4B**). However, the patients treated with PLD regimen were significantly more likely to achieve VGPR (RR 1.37, 95% CI 1.01 to 1.87; **Figure 4C**) than those treated with no PLD regimen.

*Adverse events (AEs):* The trial [10] reported AEs including neutropenia (Grade 3/4), febrile neutropenia (Grade 3/4), thrombocytopenia (Grade 3/4), anemia (Grade 3/4), cardiac events (Grade 3/4), neuropathy (Grade 3/4), nausea (Grade 3/4), hand-foot syndrome, alopecia and treatment-related deaths. Compared with the no PLD arm patients in the PLD arm were significantly more likely to experience the following (**Table 2**): neutropenia (Grade 3/4) (RR 2.03, 95% CI 1.48 to 2.79), thrombocytopenia (Grade

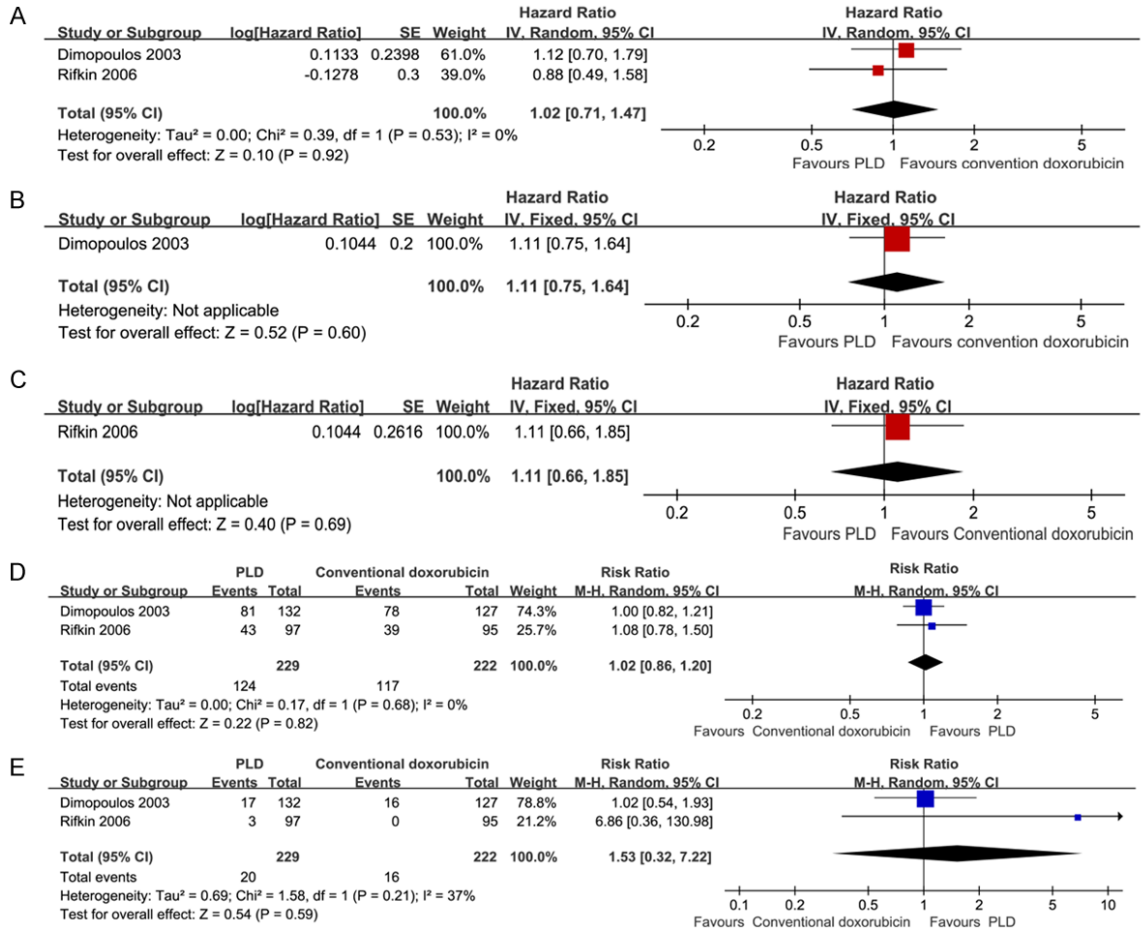


**Figure 5.** Meta-analysis of overall survival (OS), disease control and response rates in the trials comparing PLD with conventional doxorubicin. A: OS; B: Time to progression; C: Progression free survival; D: Overall responses; E: Complete responses. IV, inverse variance; M-H, Mantel-Haenszel; SE, standard error; CI, confidence interval.

3/4) (RR 1.44, 95% CI 1.04 to 2.00) and hand-foot syndrome (RR 100.38, 95% CI 6.22 to 1620.00).

However, higher the risk ratio of neutropenia (Grade 3/4) in the PLD arm did not translate into a statistically significant increase in febrile neutropenia (RR 1.49; 95% CI 0.25, 8.86). No statistically significant differences were noted between study arms in the risk ratio of other severe adverse events, including anemia (Grade 3/4) (RR 1.03, 95% CI 0.63 to 1.69), cardiac events (Grade 3/4) (RR 0.66, 95% CI 0.11 to 3.94), neuropathy (Grade 3/4) (RR 0.44, 95% CI 0.14 to 1.42), nausea (Grade 3/4) (RR 6.96, 95% CI 0.86 to 56.22), alopecia (RR 1.99, 95% CI 0.18 to 21.81) and treatment-related deaths (RR 0.71, 95% CI 0.45 to 1.13) (**Table 2**).

*Quality of evidence*

Quality of evidence was presented in **Table 2**. The quality of the currently available clinical evidence was high for OS but was moderate to very low for other outcomes.

*Comparison 2: PLD versus conventional doxorubicin*

Two trials compared PLD with conventional doxorubicin in previously untreated MM [16, 17]. OS, TTP, PFS, and response rate were reported in these trials, but not quality of life. We used previously reported methods to estimate their log (HRs) and variance for these outcomes.

*Primary outcomes*

*Overall survival (OS):* The pooled analysis showed no statistically significant difference in OS between patients with PLD and those with conventional doxorubicin (HR 1.02, 95% CI 0.71 to 1.47, P=0.92; $I^2$ for heterogeneity=0%, P=0.53; **Figure 5A**). Subgroup analyses by age

**Table 3.** Summary of findings for comparison of PLD and conventional doxorubicin for multiple myeloma

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | |
| | Conventional doxorubicin | PLD | | | |
| OS | 113 per 1000 | 115 per 1000 (81 to 161) | HR 1.02 (0.71 to 1.47) | 451 (2 studies) | ⊕⊕⊕⊕ high |
| TTP | 87 per 1000 | 96 per 1000 (66 to 138) | HR 1.11 (0.75 to 1.64) | 259 (1 study) | ⊕⊕⊕0 moderate[1] |
| PFS | 558 per 1000 | 596 per 1000 (416 to 779) | HR 1.11 (0.66 to 1.85) | 192 (1 study) | ⊕⊕⊕0 moderate[1] |
| Overall response | 527 per 1000 | 538 per 1000 (453 to 632) | RR 1.02 (0.86 to 1.2) | 451 (2 studies) | ⊕⊕⊕0 moderate[1] |
| CR | 72 per 1000 | 110 per 1000 (23 to 520) | RR 1.53 (0.32 to 7.22) | 451 (2 studies) | ⊕⊕⊕0 moderate[1] |
| AEs-Neutropenia (Grade 3/4) | 242 per 1000 | 114 per 1000 (58 to 220) | RR 0.47 (0.24 to 0.91) | 192 (1 study) | ⊕⊕⊕0 moderate[1] |
| AEs-Antibotic treatment | 392 per 1000 | 368 per 1000 (302 to 443) | RR 0.94 (0.77 to 1.13) | 451 (2 studies) | ⊕⊕⊕0 moderate[1] |
| AEs-Thrombocytopenia (≥Grade 2) | 79 per 1000 | 38 per 1000 (13 to 108) | RR 0.48 (0.17 to 1.37) | 259 (1 study) | ⊕⊕⊕0 moderate[1] |
| AEs-Anemia (Grade 3/4) | 105 per 1000 | 124 per 1000 (56 to 273) | RR 1.18 (0.53 to 2.59) | 192 (1 study) | ⊕⊕⊕0 moderate[1] |
| AEs-Cardiac events (Grade 3/4) | 0 per 1000 | 0 per 1000 (0 to 0) | RR 6.86 (0.36 to 130.98) | 192 (1 study) | ⊕000 very low[1,2] |
| AEs-Neuropathy (≥Grade 2) | 102 per 1000 | 114 per 1000 (56 to 229) | RR 1.11 (0.55 to 2.24) | 259 (1 study) | ⊕⊕⊕0 moderate[1] |
| AEs-Nausea (Grade 3/4) | 32 per 1000 | 72 per 1000 (19 to 271) | RR 2.29 (0.61 to 8.58) | 192 (1 study) | ⊕⊕00 low[1,3] |
| AEs-Hand-foot syndrome | 11 per 1000 | 258 per 1000 (36 to 1000) | RR 24.48 (3.39 to 177.1) | 192 (1 study) | ⊕000 very low[1,2] |
| AEs-Alopecia | 446 per 1000 | 245 per 1000 (169 to 352) | RR 0.55 (0.38 to 0.79) | 451 (2 studies) | ⊕⊕⊕0 moderate[1] |
| AEs-Treatment-related deaths | 113 per 1000 | 100 per 1000 (52 to 191) | RR 0.89 (0.46 to 1.7) | 451 (2 studies) | ⊕⊕⊕0 moderate[1] |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; OS, overall survival; TTP, time to disease progression; PFS, progression free survival; CR, complete response; PR, partial response; AEs, adverse events. [1]Downgraded one level due to lack of blinding (subjective outcomes are highly susceptible to biased assessment). [2]Downgraded two levels due to very low number of events, very wide CI. [3]Downgraded one level due to low number of events, wide CI.

or patient characteristics were not possible because the data were unavailable.

*Secondary outcome measures*

*Time to progression (TTP) and progression free survival (PFS):* There was no statistically significantly difference in TTP between patients treated with PLD or conventional doxorubicin (HR 1.11, 95% CI 0.75 to 1.64, P=0.60; **Figure 5B**). No statistically significant difference between the PLD arm and the conventional doxorubicin arm was noted with respect to PFS (HR 1.11, 95% CI 0.66 to 1.85, P=0.69; **Figure 5C**).

*Response rate:* Both two RCTs [16, 17] reported ORR and CR, but not VGPR. Pooled results showed that there were no statistically significant differences between arms in ORR (RR 1.02, 95% CI 0.86 to 1.20; **Figure 5D**) and CR (RR 1.53, 95% CI 0.32 to 7.22; **Figure 5E**).

*Adverse events (AEs):* Reported in these two trials were neutropenia (Grade 3/4), antibotic treatment, thrombocytopenia (≥Grade 2), anemia (Grade 3/4), cardiac adverse events (Grade 3/4), neuropathy (≥Grade 2), nausea (Grade 3/4), hand-foot syndrome, alopecia and treatment-related deaths. Compared with those receiving the conventional doxorubicin regimen, patients receiving PLD regimen had significantly higher risk of (**Table 3**): hand-foot syndrome (RR 24.48, 95% CI 3.39 to 177.10) but lower risks of neutropenia (Grade 3/4) (RR 0.47, 95% CI 0.24 to 0.91) and alopecia (RR 0.47, 95% CI 0.24 to 0.91).

Although the risk ratio of neutropenia (Grade 3/4) was higher in the conventional doxorubicin arm, antibotic treatment episodes were similar (RR 0.94; 95% CI 0.77, 1.13). No statistically significant differences were noted between study arms in other severe AEs, including thrombocytopenia (≥Grade 2) (RR 0.48, 95% CI 0.17 to 1.37), anemia (Grade 3/4) (RR 1.18, 95% CI 0.53 to 2.59), cardiac events (Grade 3/4)(RR 6.86, 95% CI 0.36 to 130.98), neuropathy (Grade 3/4) (RR 1.11, 95% CI 0.55 to 2.24), nausea (Grade 3/4) (RR 2.29, 95% CI 0.61 to 8.58) and treatment-related deaths (RR 0.89, 95% CI 0.46 to 1.7) (**Table 3**).

*Quality of evidence*

Quality of evidence was presented in **Table 3**. The quality of the currently available clinical evidence was high for OS but was moderate to very low for other outcomes.

## Discussion

To evaluate the efficacy and safety of PLD for patients with MM, we conducted a systematic search and included three RCTs [10, 16, 17] involving 1100 patients in the meta-analyses. Among these trials, one RCT involving 646 patients evaluated PLD versus no PLD, and two RCTs involving 454 patients compared PLD with conventional doxorubicin. We obtained the following results from the meta-analyses.

Compared with no PLD for patients with relapsed or refractory myeloma, PLD can prolonged TTP and PFS, increased VGPR rate, but did not confer significant benefit on OS. Subgroup analysis showed that age, cytogenetic abnormality or del(13) might not be an influencing factor for the OS effect. No statistically significant differences were found in overall response rates (ORR) and complete responses (CR). For adverse events (AEs), there was no difference between arms in the risks of grade 3/4 febrile neutropenia, grade 3/4 cardiac toxicity and treatment-related deaths, although increased the risks of grade 3/4 neutropenia, grade 3/4 thrombocytopenia and hand-foot syndrome (RR 100.38, 95% CI 6.22 to 1620.00).

Compared with conventional doxorubicin in the induction therapy of newly diagnosed multiple myeloma, there were no statistically significant differences in OS, TTP, PFS, ORR and CR. Subgroup analysis of OS by age or patient characteristics were not possible due to lack of available data. For AEs, there was no evidence for difference between arms in the risks of antibotic treatment, grade 3/4 cardiac adverse events and treatment-related deaths, although reduced the risk of grade 3/4 neutropenia and increased the risk of hand-foot syndrome.

Three published randomised controlled trials (RCTs) are included in this review of PLD treatment for multiple myeloma. All included studies published as full-text articles. The inclusion criteria of participants for all included RCTs are consistent with clinical practice in “real-world” conditions. Of the three studies included in the meta-analysis, all studies provided data on OS and response rates, two studies provided data on TTP and two studies provided data on PFS. All studies reported adverse events (AEs) data, although not for all of the individual AEs reported in this review. All these aspects increase the applicability of this systematic review and meta-analysis. We therefore conclude that the completeness and applicability of the evidence in this review to be generally moderate to high for the outcomes relevant to this review. We are aware of one ongoing study [31] from a review of clinical trials registries that may be included in a future update of this review.

The risk of bias in all three studies included in this review has been analysed in detail. These three studies were reported as RCTs and published in full-text form. Only one [16] of the included studies reported that random sequence was generated by referring to random permuted blocks, but other studies [10, 17] did not report the method of random sequence generation. Allocation was adequately concealed in one study (central allocation) [16], while not reported in two studies [10, 17] that could introduce selection bias. One trial [10] was reported as open-label study, which is more susceptible to performance bias. For another trial [16], patients were not blinded so we judged the potential risk of bias for blinding of participants and personnel to be high. For the remaining one trial [17], it didn’t reported information for blinding of participants and trial personnel. We considered the risk of bias for blinding of participants and personnel as unclear. None of the included studies provided information for blinding of the outcome assessors. This might lead to detection bias for all outcomes except OS. All included studies [10, 16, 17] explicitly provided the number of and reasons for withdrawal or loss to follow-up. We judged the three studies as low risk of attrition bias. Three studies [10, 16, 17] reported all pre-planned outcomes in the protocol and we judged them as low risk of reporting bias.

Collectively, the quality of evidence for the main comparisons of was high for for OS, and moderate for TTP, PFS or response rates because lack of blinding except OS (**Tables 2** and **3**). For adverse events, the comparison between PLD and no PLD provided low quality of evidence for grade 3/4 febrile neutropenia and grade 3/4 cardiotoxicity because of lack of blinding and low number of events with wide 95% confidence interval (CI), very low quality of evidence for hand-foot syndrome lack of blinding and very low number of events with very wide 95% CI. The comparison between PLD and conven-

tional doxorubicin provided low quality of evidence for grade 3/4 cardiotoxicity because of lack of blinding, low number of events and wide 95% confidence interval (CI), very low quality of evidence for hand-foot syndrome because of lack of blinding, very low number of events and very wide 95% CI.

To prevent potential bias, we only included RCTs in this review. We attempted to avoid biases by conducting all review processes (trial searching, data extraction and analysis) in duplicate, by two review authors working independently. Any disagreements were resolved by discussion until consensus was obtained. Therefore, we are confident that all relevant studies were identified and included and all review processes were followed according to Cochrane recommendations. However, it should be noted that we did not perform publication bias assessment because only a few trials were included in the present systematic review and meta-analysis. Furthermore, one trial was identified as ongoing and one trial was reported as complete in 2009 but not yet published, therefore we could not include data from these trials in this review.

This is the first systematic review and meta-analysis of RCTs evaluating PLD for multiple myeloma. Compared with no PLD for patients with relapsed or refractory myeloma, PLD can inhibit disease progression and increase VGPR rate, but does not improve survival. However, haematological adverse events, such as neutropenia and thrombocytopenia, occur more frequently with PLD. The currently available evidence suggests that there is no evidence for a difference between PLD and conventional doxorubicin used in induction therapy, although PLD reduced the risks of grade 3/4 neutropenia. Therefore, evidence from this review showed that an increased TTP, PFS and VGPR rate and acceptable safety with PLD as compared with no PLD for relapsed or refractory myeloma, but there is no evidence for the difference between PLD and conventional doxorubicin for patients with newly diagnosed multiple myeloma.

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## Disclosure of conflict of interest

None.

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