Memorial Sloan Kettering Cancer Center

NCI-MSK collaboration: a formal MRD meta analysis

Ola Landgren, M.D., Ph.D.
Chief of Myeloma Service, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College, New York

New York, June 24, 2016

Memorial Sloan Kettering Cancer Center

Background

- With older myeloma drugs only a smaller fraction of patients obtained a complete response (CR)

- Using modern combination therapies, 100% of patients achieve a treatment response (overall response) with up to 80% of these patients reaching a CR

Landgren et al. *(in press)*

Background (*cont.*)

- Necessary and logical step forward, studies on minimal residual disease (MRD) and its correlation with clinical outcomes

- Both progression-free survival and overall survival have been associated with MRD

- We have done a formal meta-analysis on MRD

Landgren et al. *(in press)*

Methods

- On December 22, 2015, we conducted a systematic search for clinical trials of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes

- We applied the following MEDLINE (via PubMed), EMBASE, and Cochrane's Central Register of Controlled Trials (CENTRAL)

Landgren et al. *(in press)*

Methods (*cont.*)

- Total of 390 potential studies were first identified; however, after careful review of each individual abstract, we excluded 370 since they were not clinical trials with MRD assessment in multiple myeloma

- Thus, 20 studies clinical trials of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes

Landgren et al. *(in press)*

Methods (*cont.*)

- All the 20 published studies did not include all details required for our pre-planned statistical analysis so we contacted the corresponding authors to obtain hazard ratio (HR) estimates and corresponding confidence intervals (CI) for the association between MRD and clinical outcomes

Landgren et al. *(in press)*

Methods (*cont.*)

- The meta-analysis was conducted using a random effects model, which weighted studies using the inverse-variance method

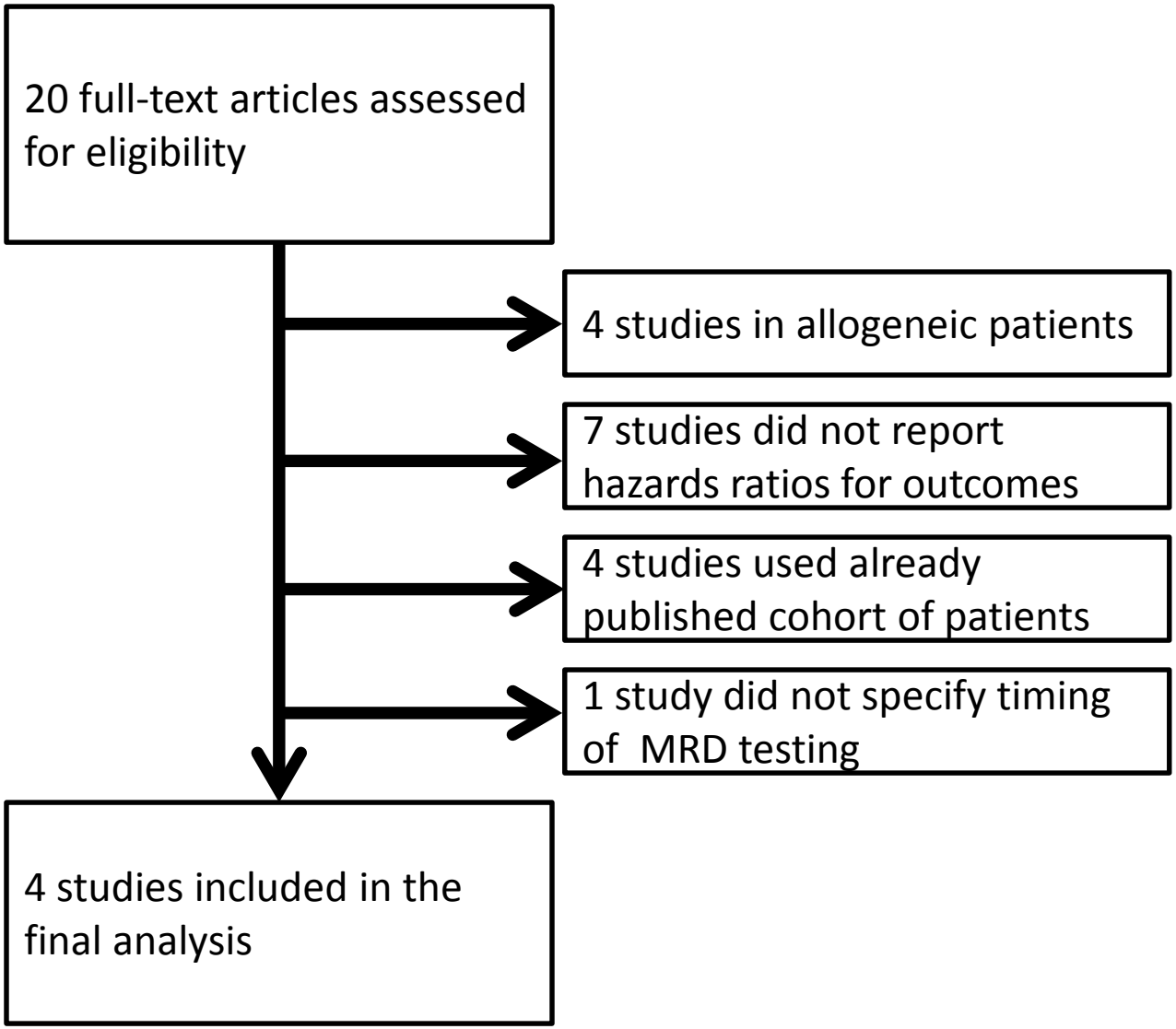
- Studies were combined on the scale of the logarithm of the hazard ratio and the corresponding standard error. The analysis used the package 'metafor' in R Statistical Platform, v 3.2.3

Landgren et al. *(in press)*

Results

- Upon careful review of the 20 identified studies, 4 studies were excluded because they reported allogeneic transplantation; 7 were excluded because they did not evaluate the association between MRD status and PFS/OS; 4 were excluded because they analyzed overlapping cohorts of patients (duplicates); and 1 was excluded because the timing of MRD analysis was not specified

Landgren et al. *(in press)*



Landgren et al. *(in press)*

Results

- Four studies with information on MRD status and HR for progression-free survival were included in the final analysis; three studies had information on overall survival (however, one study had no deaths during the original follow-up window) so two studies provided hazards ratios for overall survival

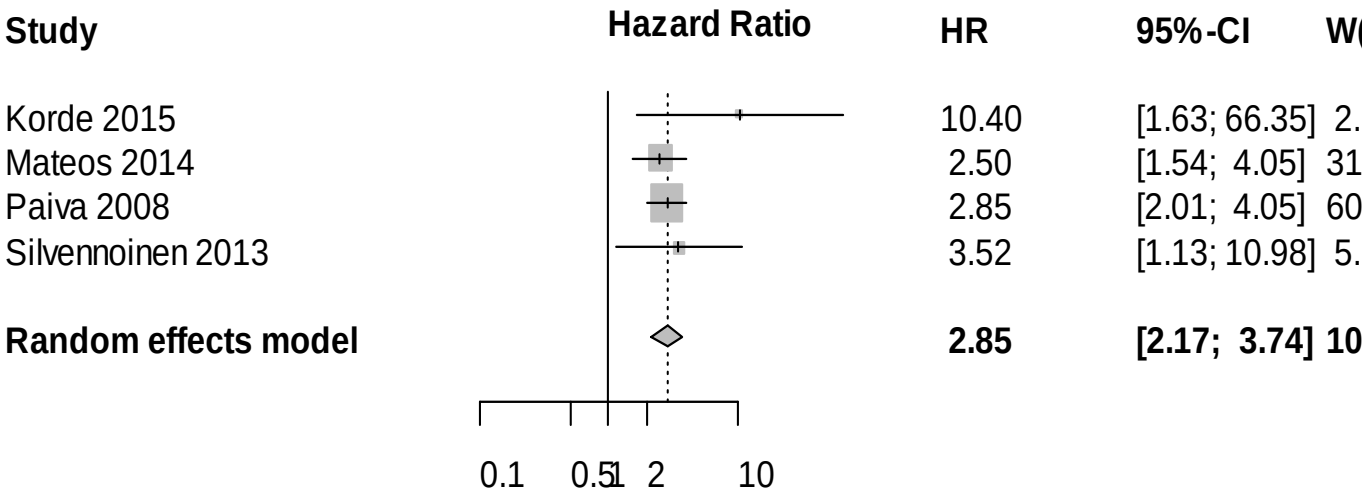
Landgren et al. *(in press)*

Results

- Three studies used multiparameter flow-cytometry and one study used allele-specific quantitative polymerase chain reaction, both with a sensitivity of at least 1 in 10,000 cells (10^{-4}) to determine MRD status
- The largest study (Paiva et al.) had the largest weight (W random = 60.4%) in the meta-analysis; and the smallest study (Korde et al.) had the smallest weight (W random = 2.2%)
- Overall, the meta-analysis show that, compared to who achieved MRD negativity, patients who remained MRD positive had worse progression-free survival (HR=2.85; 95% CI 2.17-3.74; P<0.001)

Landgren et al. *(in press)*

MRD positivity (compared to MRD negativity) and progression-free survival*



A higher hazard ratio indicates increased risk for each survival endpoint (i.e. risk of progression)

Landgren et al. *(in press)*

Memorial Sloan Kettering Cancer Center

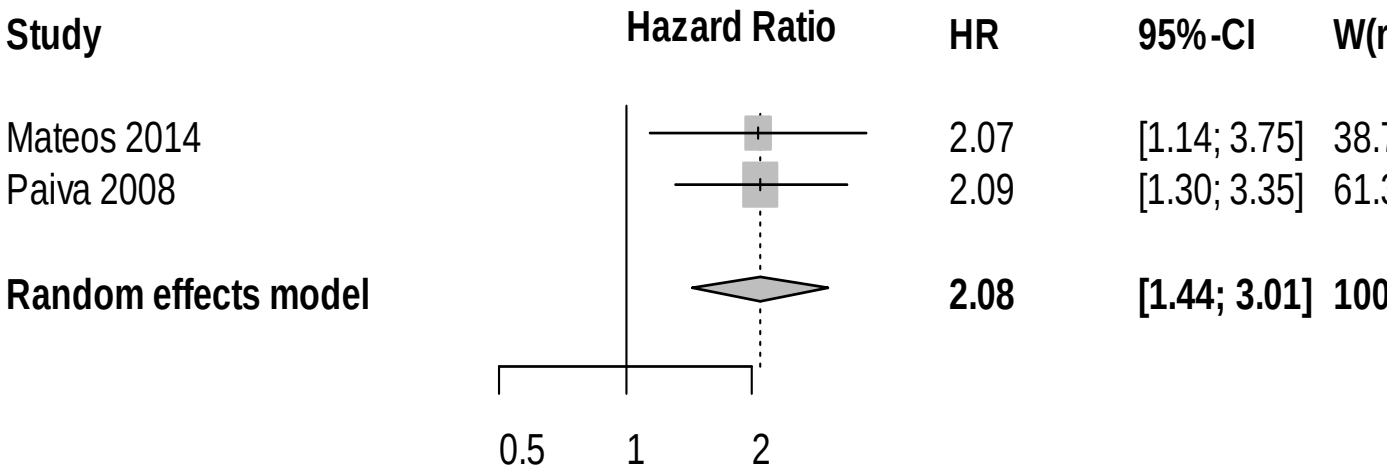
Results

- The studies by Paiva et al. and Mateos at al. were the only two that provided hazards ratios for overall survival

- Based on these two studies, our meta-analysis showed that remaining MRD positive was associated with a higher risk of death (HR=2.08; 95% CI 1.44-3.01; P<0.001)

Landgren et al. *(in press)*

MRD positivity (compared to MRD negativity) and overall survival*



A higher hazard ratio indicates increased risk for each survival endpoint (i.e. risk of dying)

Landgren et al. *(in press)*

Summary and conclusions

- This meta-analysis show that MRD negativity is associated with better progression-free survival and overall survival in newly diagnosed multiple myeloma.

- Supportive of MRD assessment becoming a surrogate clinical endpoint that could be used to support regulatory purposes for drug review in multiple myeloma

Thank you for your attention!

Ola Landgren, M.D, Ph.D.
Professor of Medicine
Chief, Myeloma Service
Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, NY 10065, USA
Email: landgrec@mskcc.org
Phone: 212-639-5126