treatment related mortality (risk ratio 1.026; 95% CI 0.01-102.118; *P*=0.991).

The results presented here are an important addition to and complement the systematic review by Gurion *et al.*[1] They provide greater precision to the existing results and the supplemental analyses, which in turn will be helpful in making informed decisions on the choice of an optimal HMA for the treatment of MDS in the absence of randomized comparisons.

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Key words: myelodysplastic syndrome, hypomethylating agents, 5-azacitidine, decitabine.

AK, AFL, and BD received honoraria from Celgene Corporation.

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Citation: Kumar A, List AF, Hozo I, Komrokji R, and Djulbegovic B. Decitabine versus 5-azacitidine for the treatment of myelodysplastic syndrome: adjusted indirect meta-analysis. Haematologica. 2010; 95(1):340-342. doi: 10.3324/haematol.2009.017764

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Meta-analysis on hypomethylating agents in myelodysplastic syndromes

The addition of hypomethylating agents into the armatorium against myelodysplastic syndromes (MDS) is commonly accepted as a promising new therapeutic option in this otherwise frustrating field. However, due to methodological aspects, it is still the subject of debate whether these compounds prolong survival when compared to other treatment modalities in this population.

Meta-analysis is an important tool for summarizing scientific data from different sources and may be of great help in clinical decision making, guideline development and the conception of new trials. In order to obtain meaningful and valid results from such investigations, it is of utmost importance that a high level of unbiased analytical accuracy is ensured.

We have read the recent work of Gurion *et al.*[1] with great interest and would like to express our concerns with respect to the applied methodology which, in our eyes, does not support the conclusion given in the title.

Using the sources cited in the above publication, we were unable to reconstruct the meta-analysis for overall survival (OS). For the trial of Silverman and co-workers[2] we estimated the hazard ratio (HR) to be 0.80 (95% confidence interval 0.57-1.12) for the intention-to-treat (ITT)-analysis and not 0.52 (0.32-0.86) as given by Gurion *et al.* Our result is in line with the original publication which states that median survival had a *P* value of 0.10. Using our estimate, the final result of the meta-analysis for OS is 0.74 (0.57-0.96) instead of 0.66 (0.55-0.80).

For the interpretation of these calculations, the cited study of Kantarjian *et al.* must be considered[3] where it reads: "The ITT-analysis […] indicates that median survival was not significantly different […] *P*=0.636." While there is insufficient information to calculate a HR, it seems plausible that the addition of this trial may change the result of the meta-analysis to a non-significant result. In our opinion, the problem of missing data is a shortcoming of the presented OS meta-analysis and we regret that this important point has not been discussed by the authors.

Instead, in the Discussion section, the authors mention only a few limitations of the data. This again might be a consequence of the fact that the quality assessment in this analysis was limited to randomization (sequence generation, allocation concealment) and blinding. As a crossover between trial arms after randomization as in the Silverman study may be an important source of bias, this is especially relevant. More generally, the completeness of the outcome data was not discussed. In addition, another important source of bias called *selective outcome reporting* may be a reason for the differences in the choice of response criteria. The choice of the outcome time to transformation to acute myeloid leukemia (AML) is potentially problematic due to its dependence on AML definitions used. For example, 32% of patients in the trial of Fenaux and co-workers had AML according to the WHO criteria at the beginning of the study.[4] Lastly, the high heterogeneity observed (even if a random effects analysis was performed) also limits the strength of the evidence and should, therefore, be given more consideration.

Aside from these issues, there are several errors in the Methods section. Based on the Results section, we conclude that the authors accepted any response definition used by the authors and not only the criteria of the International Working Group (IWG).[5] The method of meta-analysis used was the "generic inverse variance

method" and not Peto's method. Moreover, the very brief quality assessment appears to be based on the 4th version of the Cochrane Handbook and not on version 5 which was implemented in 2008.[6] Thus, for example, the new handbook requires a citation in order to justify the judgment of each quality item in a *risk-of-bias assessment*. Furthermore, the electronic search given in the paper of Gurion *et al.* was not carried out according to general recommendations. Among others, MeSH terms were not used and the EMBASE was not searched. We have not assessed whether a wider search would have increased the number of included studies.

In summary, even a rough review of the presented meta-analysis and the included trials reveals many methodological shortcomings. A correction of the major errors in the meta-analysis of overall survival and its interpretation should change the conclusion of the meta-analysis into: "*Currently it is unclear whether newer hypomethylating agents improve overall survival in MDS*." We, therefore, strongly recommend that this meta-analysis should not be used as a basis for clinical decision making or guideline development.

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Citation: C Herbst, K Bauer, and K-A Kreuzer. Decitabine versus Meta-analysis on hypomethylating agents in myelodysplastic syndromes. Haematologica. 2010; 95(1):342-343. doi: 10.3324/haematol.2009.019216

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5-azacitidine prolongs overall survival in patients with myelodysplastic syndrome - systematic review and meta-analysis (Reply to Kumar *et al.* and to Herbst *et al.*)

We read with interest the meta-analysis of Kumar *et al*.[1] and the correspondence of Herbst *et al*.[2] The former supports our meta-analysis, recently published in this journal.[3] Although both Kumar's and our meta-analysis show overall survival benefit with 5-azacitidine in patients with myelodysplastic syndrome (MDS), they differ with respect to several aspects.

First, the pooled effect of all hypomethylating agents on overall survival in our study was statistically significant [HR of 0.72, 95% CI 0.60 - 0.85] as opposed to Kumar *et al*. [HR of 0.82, 95% CI 0.64 - 1.06]. This difference may be related to different statistical methods used to pool the results, and the additional inclusion of survival data obtained from the study published by Kantarjian *et al*.[4] in the analysis of Kumar *et al*. Since we expected to retrieve only few primary studies with a small sample size, we selected to use the fixed effect model for estimation of the overall effect on survival as the most appropriate method. Second, while according to Kumar *et al*. there was no statistically significant increase in treatment related mortality (TRM)[RR of 2.47, CI 0.48-12.73], we found a significant relative risk of 7.27 with 95% CI 1.67 - 31.64. This disparity stems from different definitions of this outcome. Since we restricted our TRM data to fatal events directly related to hypomethylating agents in the primary studies and did not include in this analysis early mortality or on trial mortality data, we could not include mortality data from Kantarjian *et al*. who did not report on TRM separately. Another distinction between our meta-analysis and Kumar's is that we included only analyses of randomized controlled trials and avoided indirect comparisons which compare between observational findings across trials and thus suffer from the pitfalls of observational studies. Indirect comparisons should be interpreted cautiously unlike those of well balanced groups. This is especially true considering the four trials included in the meta-analyses where there were variations in case definitions of the population and in the response rate of the control groups. We thank Kumar *et al*. for pointing out an error in one of the primary studies[5] which we corrected, resulting in a change of the HR for overall survival from HR of 0.66, 95% CI 0.55-0.80 to HR 0.72, 95% CI 0.60-0.85. Despite the slight differences between the two meta-analyses, the resemblance between them further strengthens our results and supports the role of hypomethylating agents in MDS.

We agree with the correspondence of Herbst *et al*.[2] that systematic reviews and meta-analyses should be prepared using explicit methods to increase their accuracy and should be read critically, and we would like to respond to the issues raised.

Regarding the main outcome of overall survival, despite our efforts to get additional information from authors, we did not have sufficient data to include the data from Kantarjian *et al*. in this analysis.[3,4] This point, as well as the possible heterogeneity between trials, is thoroughly discussed in both the Results and the Discussion sections.[3] Yet, the benefit of 5-azacytidine for patients with myelodysplastic syndrome (MDS) shown in our meta-analysis is reproducible as supported by the report of Kumar *et al*.[1] Crossover between trial arms after randomization was observed only in the study published by