Reviewer's report

Title: Association Between Delayed Initiation of Adjuvant Chemotherapy and Survival in Breast Cancer: A Systematic Review and Meta-analysis

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Reviewer: Vassilis Georgoulias

Reviewer's report:

The “Association Between Delayed Initiation of Adjuvant Chemotherapy (AC) and Survival in Breast Cancer: A Systematic Review and Meta-analysis” is a well written manuscript. The authors examined the impact of the time between surgery and the initiation of adjuvant chemotherapy on the survival of breast cancer patients. The study is well designed and conducted. This meta-analysis comes to the conclusion that the delay of AC is associated with decreased survival. The limitations of the study are addressed and discussed by the authors. To my knowledge, this is the first meta-analysis regarding the association of timing of AC for breast cancer and survival reported as a full paper. However, as acknowledged by the authors, a large proportion of the patients that were included to the analysis were treated with CMF, an old-fashioned regimen. No patients (or a minority - see comment #3) received taxanes. It is unclear whether the findings of the study can be extrapolated to the current standard of AC or address a significant issue that should be investigated in (prospective, if possible) studies with the use of the more modern regimens (dose dense, taxanes, etc.). Therefore, I would suggest that the manuscript is more appropriate for BMC Cancer.

The following minor comments should be addressed by the authors:

1) It should be stressed that the meta-analysis examines a mixed patient population, in terms of nodal, hormone receptor and menopausal status. Though most of the included studies had performed adjustments for those factors, is the effect of AC delay on survival the same for patients with infiltrated lymph-nodes and those without, or for pre- and postmenopausal women?

2) In the Eligibility and validity of literature-based data section it is stated that “first, the relevant prognostic factors were adequately described between comparator groups; second, either the comparison groups were balanced for the relevant prognostic factors, or the reported results were adjusted for other prognostic factors”. However (Table 1), in the study by Samur et al. no adjustment for covariates had been made, and in the study by Kerbrat et al. the adjusted factors had not been reported. In the footnote of Table 1, the authors state that "although this study (Samur et al) had an unadjusted HR, we did not exclude this study with negative outcome to increase the reliability of positive results of meta-analysis". It should be mentioned in the Results section.
3) In the studies by Hershman et al. and Nurgalieva et al. (Table 1), which were the AC regimens administered? Did any patients (and if yes, at which percentage) receive taxanes?

4) It should be more clear which percentage of the whole patient population received CMF or anthracycline-based AC. Was there a different impact of AC delay on survival, in patients administered CMF vs. those treated with anthracycline-based AC?

5) The studies cited in the Discussion (Buzdar et al, Shannon et al, Sanchez et al, Alkis et al, Altundag et al) were not included in the meta-analysis due to low validity. The specific reasons for the exclusion of those studies could be mentioned. For example, in the study by Shannon et al the analysis was adjusted for prognostic factors. Why was this study not considered of high validity and not included in the meta-analysis? The authors could make more clear the definition of high and low validity.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests