Review of: "On the Need for Better Information from Randomized Clinical Trials in Oncology"

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Potential competing interests: No potential competing interests to declare.

The article deals with the interesting topic of the methodology of randomized clinical trials, in this case on oncology drugs. The calculation of relative and absolute risk with the data obtained in clinical trials is interesting, since it provides additional information. However, I believe that the structure could be improved and some of the data corrected as detailed below.

It is suggested to specify the data obtained directly from the article or the supplementary appendix, and the data elaborated by the authors of the manuscript (calculated RR and AR). Likewise, it is suggested to express the calculated data with 2 decimals, when it's possible, to facilitate reading comprehension.

Abstract section

There are no suggestions for change.

Introduction section

First paragraph. It is suggested to: clarify the importance of getting the right answers from clinical trials for both patients and the physicians treating them, as mentioned in the introduction. I suggest considering the utility of the information from the perspectives of public health, the attending physician, and the patient.

Second paragraph. It is suggested to: add a section of materials and methods employed where the methodology used is explained in more detail. That section could explain how the articles were selected, who analysed them, and how the relative and absolute risk was calculated (with the link to calculators mentioned).

Published RCTs in the NEJM section

1st study, first paragraph. It is suggested to change the text to: The first study compared belzutifan and everolimus in patients with advanced renal cell carcinoma. This study enrolled 374 patients receiving belzutifan and 372 receiving everolimus. The dual primary endpoints were progression-free survival (PFS) and overall survival (OS). The primary

analysis of PFS occurred at the first interim analysis, which was planned to be performed after approximately 563 participants had had disease progression or had died and approximately 7 months after the last participant had undergone randomization. Interim analyses of OS occurred at the first interim analysis and at the second interim analysis, which was planned to be performed after approximately 410 participants had died and approximately 17 months after the last participant had undergone randomization. It was calculated that a sample size of 736 participants would provide the trial with approximately 96.9% power to detect a hazard ratio of 0.70 for disease progression or death in the analysis of progression-free survival, at an initially assigned two-sided alpha level of 0.010 after approximately 626 events had occurred. In the same way, for OS, it was calculated that there was approximately 85.4% power to detect a hazard ratio of 0.75 for death at the final analysis of overall survival, at an initially assigned two-sided alpha level of 0.038 after 483 deaths had occurred.

In the first interim analysis, at a median follow-up time of 18.4 months, the median PFS was 5.6 in both arms (95% CI 3.9-7 and 4.8-5.8 respectively) with a HR of 0.75 (95% CI 0.63-90); however, curves crossed, breaking the proportional hazards assumption. The estimated percentage of participants who were alive and progression-free at 6 months, 12 months, and 18 months were 46.6%, 33.4%, and 24.0% in the belzutifan group, while in the everolimus group they were 42.5%, 17.1%, and 8.3%.

For OS, at the second interim analysis, 213 participants (57.0%) in the belzutifan group and 228 participants (61.3%) in the everolimus group had died. The estimated percentage of participants who were alive at 12 months and 18 months were 67.9% and 55.2% in the belzutifan group, and 65.8% and 50.6% in the everolimus group, respectively. The median OS was 21.4 months in the belzutifan group and 18.1 months in the everolimus group (HR for death, 0.88; 95% CI, 0.73-1.07; p=0.20).

1st study, second paragraph. It is suggested to change the text to: The number of PFS events, described in the Supplementary Appendix of the article, was 289/374 and 276/372 in the group receiving belzutifan and everolimus respectively. With these event numbers, a RR of 1.0415 has been calculated, which translates into an increase of Relative Risk (RR) for progression of 4.15% (95% CI 0.96 - 1.13; p=0.98), with an increase of Absolute Risk (AR) for progression of 3.08% (95% CI, -3.07 to 9.23). Accordingly, the number needed to harm (NTH) is 32.

According to data shown in the article, at the second interim analysis, 213 participants in the belzutifan group and 228 participants in the everolimus group died. With these event numbers, the RR and AR for death have been calculated. The numbers are: RR 0.9292 (95% CI 0.82 - 1.05), a reduction of 7.08%, p=0.23, while the AR reduction is 4.34% (-2.71% to 11.39%), both lack statistical significance. The number needed-to-treat (NNT) is 23 (95% CI, 8.8-Infinity).

2nd study, first paragraph. It is suggested to change the text to This study evaluated the efficacy of adjuvant osimertinib versus placebo following chemoradiation in patients with Stage III EGFR-mutated non-small cell lung cancer. Patients underwent randomization in a 2:1 ratio to receive osimertinib or placebo, until disease progression (Progression-free survival was the primary end point). A total of 216 patients underwent randomization; 143 were assigned to receive osimertinib, and 73 were assigned to receive placebo. For the primary analysis, it was calculated that 120 events of disease progression or death would provide the trial with 90% power to detect a hazard ratio of 0.53 at a two-sided 5%

significance level.

The results showed a significant PFS benefit with osimertinib, as the median PFS was 39.1 months compared to 5.6 months with placebo, and the HR was 0.16 (95% CI, 0.10-0.24; p<0.001). The percentages of the patients who were alive and progression-free at 12 months and 24 months were 74% and 65% with osimertinib, and 22% and 13% with placebo respectively. Beginning with the first post-baseline scan, Kaplan–Meier curves showed early separation between the treatment groups, a separation that was sustained throughout follow-up.

Overall survival was one of the secondary end points established. As of the data cut-off date, 28 patients (20%) had died in the osimertinib group and 15 patients (21%) in the placebo group (a total of 43 patients had died). Interim data revealed a 36-month OS among 84% of patients with osimertinib and 74% with placebo, with a HR for death of 0.81 (95% CI, 0.42-1.56; p=0.53), which was not significant at this interim analysis.

2nd study, second paragraph. It is suggested to change the text to: According to the data in the article, the study reported a total of 120 events of disease progression or death: 57 events out of 143 in the osimertinib group and 63 out of 73 in the placebo group. With these event numbers, the RR and AR have been calculated, obtaining a RR reduction for progression of 46.2% (95% CI: 0.37 - 0.58; p<0.0001) and an AR reduction of 46.4% (95% CI: 35.19 - 57.69%). This data indicate a high efficacy of osimertinib, with a NNT of 2, meaning that treating two patients with osimertinib is required to prevent one progression event.

2nd study, third paragraph. It is suggested to change the text to: However, the impact on mortality is less pronounced, with 28 patients dying out of 143 in the osimertinib group and 15 patients out of 73 in the placebo group (data obtained from overall survival in the Supplementary Appendix). With these event numbers, the RR and AR for death have been calculated. The calculated RR is 0.9529 (95% CI 0.5442-1.6686; p=0.866), a reduction of 4.71%, which is not statistically significant, while the AR reduction is 0.97% (95% CI, -10.36 to 12.29%), which is not statistically significant either. Consequently, the NNT to prevent one death is 103 (95% CI, 8.1-Infinity), indicating that 103 patients would need to be treated with osimertinib to avoid one death.

3rd study, first paragraph. It is suggested to change the text to: In this study, the efficacy of tisotumab vedotin as second or third-line therapy for recurrent cervical cancer was evaluated in contrast to receiving standard treatment with chemotherapy. A total of 502 patients were randomized in a 1:1 ratio, with 253 assigned to receive tisotumab vedotin and 249 assigned to receive chemotherapy. The primary endpoint was OS. The investigators planned to enrol approximately 482 patients, and they calculated that the occurrence of 336 total deaths would provide the trial with an overall power of 90%. A prespecified interim efficacy analysis was performed when approximately 75% of the total number of events (252 of 336 events) had occurred.

At the planned interim analysis, with a median follow-up time of 10.8 months and 263 deaths having occurred, the median OS was significantly longer in the tisotumab vedotin group than in the chemotherapy group, with 11.5 months vs. 9.5 months, results that represented a 30% lower risk of death with tisotumab vedotin than with chemotherapy (HR, 0.70; 95% CI, 0.54- 0.89; p=0.004).

3rd study, second paragraph. It is suggested to change the text to: As shown in the OS curve (Figure 2 in the article), the number of events was 123/253 and 140/249 for the tisotumab vedotin and chemotherapy groups, respectively. With this data, the RR and AR have been calculated. The RR is 0.8647 (95% CI 0.73-1.0224; p= 0.0889), which means a relative reduction of 13.53%, while the AR is 7.61% (95% CI -1.10% to 16.32%) for a NNT of 13 (95% CI 6.1-Infinity). Neither the RR nor the AR reductions are statistically significant.

On the other hand, there were 198/253 and 194/249 disease progression events for tisotumab vedotin and chemotherapy, respectively. With these numbers, the RR and AR calculated are (RR= 1.0045) higher in the tisotumab vedotin group, with a relative risk increase of 1.45% (95% CI 0.91-1.10; p=0.095) and an absolute risk increase of 0.35% (95% CI, -6.89% to 7.59%). Therefore, both data are not statistically significant.

4th study, first paragraph. It is suggested to change the text to: This RCT involved patients with previously untreated EGFR-mutated advanced NSCLC. They were randomized in a 2:2:1 ratio, with 429 patients in the amivantamab-lazertinib group, 429 in the osimertinib group, and 216 in the lazertinib group. The primary endpoint was PFS in the amivantamab-lazertinib group as compared with the osimertinib group. For the calculation of PFS, they estimated that a sample of at least 800 patients with 450 events across the amivantamab-lazertinib and osimertinib groups would provide the trial with 90% power to detect a hazard ratio for progression or death of 0.73 with a two-sided alpha of 0.05. One futility analysis and one interim analysis were conducted as planned when approximately 120 and 280 progression-free survival events occurred, respectively, from the amivantamab-lazertinib and osimertinib groups combined. An interim analysis of overall survival (a secondary endpoint) was planned to be conducted at the time of the primary analysis of PFS (OS was to be analysed with an overall type I error rate of 0.05 given that the statistical significance in PFS was achieved).

At a median follow-up time of 22 months, the median PFS was 23.7 months in the amivantamab-lazertinib group, as compared with 16.6 months in the osimertinib group. The median PFS was significantly longer in the amivantamab-lazertinib group, with a HR of 0.70 (95% CI, 0.58-0.85; p<0.001). The percentage of patients who were alive and free from disease progression was 60% at 18 months and 48% at 24 months in the amivantamab-lazertinib group, and 48% at 18 months and 34% at 24 months in the osimertinib group.

The median OS could not be estimated in either group. With 97 patient deaths in the amivantamab-lazertinib group and 117 in the osimertinib group (a total of 214 deaths reported across both groups), the HR for death for the combination treatment was 0.80 (95% CI, 0.61-1.05).

4th study, second paragraph. It is suggested to change the text to: The number of events in the PFS outcome was 192/429 in the amivantamab-lazertinib group and 252/429 in the osimertinib group, as shown in the article. With these numbers, the RR calculated is 0.7619, translating to a reduction in progression of 23.81% (95% CI 0.67-0.87; p=0.0001), and the AR reduction calculated for progression is 13.99% (95% CI 7.36%-20.61%), both statistically significant. This corresponds to a NNT of 7 (95% CI, 4.9%-13.6%).

With data shown in the article, a total of 97 patients in the amivantamab-lazertinib group and 117 in the osimertinib group

died (out of 429 patients in each group). The calculated RR is 0.8291 (95% CI, 0.66-1.05; P=0.11), which translates to a relative risk reduction of 17.09%; the AR reduction is 4.66% (95% CI -0.011 to 0.104) with an NNT of 21, so that they are not statistically significant.

5th study, first paragraph. It is suggested to change the text to: In this randomized controlled trial (RCT) evaluating adjuvant therapy in resected stage III melanoma patients harbouring BRAFV600 mutations, 438 patients were allocated to the dabrafenib plus trametinib arm for 12 months, while 432 patients were assigned to the placebo arm. The primary end point was relapse-free survival, and overall survival was one of the secondary end points included. The final analysis of OS was conducted after the results for relapse-free survival were found to be significant, in accordance with a hierarchical approach. The trial was to be considered complete, and the final analysis of overall survival was to be conducted when 260 patients had died or at the cut-off date (July 31, 2023), whichever occurred first. With 260 events, the trial had approximately 80% power to detect a hazard ratio for death of 0.70.

5th study, second paragraph. It is suggested to change the text to: At the end of the trial, the median duration of follow-up was 8.33 years for dabrafenib plus trametinib and 6.87 years for placebo. Median relapse-free survival favoured dabrafenib plus trametinib, with 93.1 months vs 16.6 months in the placebo group; the hazard ratio for relapse or death was 0.52 (95% CI, 0.43 to 0.63). According to the number of events described (198/438 in the treatment group and 264/432 in the placebo group), a RR of 0.7397 has been calculated, which translates to a reduction of 26.03% (95% CI, 0.65-0.84; p<0.0001), whereas the AR reduction has been 15.91% (95% CI, 9.36-22.45) for a NNT of 6 (95% CI, 4.5-10.7). Both risks are statistically significant.

The estimated OS at 8 years was 71% with dabrafenib plus trametinib (125 events out of 438) and 65% with placebo (136 events out of 432); the hazard ratio for death was 0.80 (95% CI, 0.62 to 1.01; p=0.06), as described in the article. The RR calculated has been 0.9065, a reduction of 10% (95% CI 0.74-1.11; p=0.3440), whereas the AR reduction has been 2.94% (95% CI -3.15 to 9.03) and a NNT of 34 (95% CI, 11.1 to Infinity). Both risk reductions had no statistical significance.

Comments section

In “Table 1. Hazard Ratio, Relative Risk and Absolute Risk reductions and NNT for survival”, correct the data obtained if the previous suggestions are accepted.

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