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Letter

Reply to the Letter to the Editor by Hughes in response to the article entitled "Multicentre randomised Phase III study comparing the same dose and schedule of cisplatin plus the same schedule of vinorelbine or gemcitabine in advanced NSCLC", published in vol. 41 Issue 1 of the *European Journal of Cancer*

Sir,

It is the result of direct observation, and not of inference, that cisplatin plus vinorelbine (CP + VNR) was cheaper overall compared to cisplatin plus gemcitabine (CP + GEM), in the perspective of our hospital.

As to inference, the first concern raised by Hughes, i.e., the statement that "it is inappropriate to conduct a cost-minimisation analysis (CMA) on the basis of an observed lack of significance in regimen efficacies" is simply not applicable to our study. The issue is not a lack of significance, but a lack of effect. The paper clearly indicates that our study was designed to demonstrate the superiority of CP + GEM *vs.* CP + VNR (effect), and powered to do so at the conventional levels of confidence (statistical significance). In this case there is "evidence of absence", because the effect itself was not detected, not even as a point estimate, not to mention intervals of confidence or significance. Indeed, contrary to our original hypothesis, CP + VNR was superior to CP + GEM, with a point estimate of the primary end point (overall response rate) of 32.1% *vs.* 26.7%. Moreover, the use of a cost effectiveness analysis, as suggested by Hughes, in order to take into account differential safety or tolerability, is not appropriate. How can it be possible to combine two different and non-homogeneous measures – effectiveness and safety – into a single natural unit, which is the common denominator of a cost effectiveness analysis [1]? It is as reasonable as mixing apples and oranges. Cost utility or cost benefit analyses are appropriate but they could not be applied, since, at the time in which the trial was started, suitable and practical tools of measurements were not available or were not validated for Italy.

Hughes, by quoting a paper of Thompson and Barber [2], raises also concerns about the use of Mann-Whitney *U* test and the shape(s) and location(s) of the distributions of cost. The agreement around the non-appropriateness of the Mann-Whitney *U* test for comparing costs is far from general. Nonetheless, the application of an alternative approach [2] generate a Student's *t*-test statistic value greater than 17 for the comparison of mean total costs between CP + VNR and CP + GEM, which is associated to a $P < 0.00000000000000000000000000001$ (30 zeros after the point, *i.e.*, less than one probability out of thousands of billions of billions of billions of billions). Similar results were obtained using bootstrap techniques, another more recent alternative approach suggested [2]. At least in our study, the Mann-Whitney *U* test is slightly more conservative, as it is associated with only 23 zeros after the point. The figure below shows the actual distribution of total costs in the two arms. It is evident that the distributions seem to have "significantly" different locations, with the one of CP + GEM located some 2000 Euro (2.018€, bootstrap 95% confidence intervals €2.244 – €1.792) to the right (*i.e.*, more costly) of the distribution of CP + VNR. Moreover, the use of both Student's *t* and bootstrap test for the comparisons the cost of adverse reactions generated *P* values that are not significant at conventional levels ($P = 0.1$). The original paper, therefore, provided the reader with extremely conservatives estimate of the savings that can be achieved with CP + VNR compared to CP + GEM.

For the above reasons, we believe that the pharmacoeconomic analyses we conducted are appropriate to the objective of our study and the perspective considered, exposing the reader to indeed conservative estimates. We also think that decision makers, at least those to which our evidence can be transferred, should be confident that CP + VNR is less costly than CP + GEM in patients with advanced non-small cells lung cancer, without being less efficacious. Concerns regarding safety and efficacy-safety trade-offs deserve further – solid-research, as suggested by recent work on prostate cancer [3].

References

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